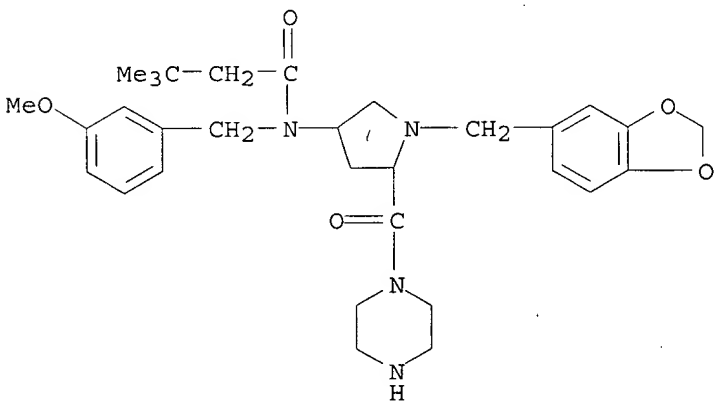
L3 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN **334998-27-5** REGISTRY
CN Butanamide, N-[1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C31 H42 N4 O5
SR CA
LC STN Files: CA, CAPLUS, CHEMCATS, TOXCENTER, USPATFULL

Ring System Data

Elemental Analysis EA	Elemental Sequence ES	Size of the Rings SZ	Ring System Formula RF	Ring Identifier RID	RID Occurrence Count
C4N	NC4	5	C4N	16.136.1	1
C6	C6	6	C6	46.150.18	1
C4N2	NC2NC2	6	C4N2	46.383.1	1
C3O2-C6	OCOC2-C6	5-6	C7O2	333.584.8	1



elected Species

Calculated Properties (CALC)

PROPERTY (CODE)	VALUE	CONDITION	NOTE
Bioconc. Factor (BCF)	1	pH 1	(1) ACD
Bioconc. Factor (BCF)	1	pH 4	(1) ACD
Bioconc. Factor (BCF)	12.1	pH 7	(1) ACD
Bioconc. Factor (BCF)	101	pH 8	(1) ACD
Bioconc. Factor (BCF)	182	pH 10	(1) ACD
Boiling Point (BP)	714.1+/-60.0 deg C	760.0 Torr	(1) ACD
Enthalpy of Vap. (HVAP)	104.38+/-3.0 kJ/mol		(1) ACD
Flash Point (FP)	385.7+/-59.2 deg C		(1) ACD
H acceptors (HAC)	9		(1) ACD
H donors (HD)	1		(1) ACD
Koc (KOC)	1	pH 1	(1) ACD
Koc (KOC)	1	pH 4	(1) ACD
Koc (KOC)	95.7	pH 7	(1) ACD

Koc (KOC)	799	pH 8	(1) ACD
Koc (KOC)	1440	pH 10	(1) ACD
logD (LOGD)	-1.72	pH 1	(1) ACD
logD (LOGD)	-1.68	pH 4	(1) ACD
logD (LOGD)	2.10	pH 7	(1) ACD
logD (LOGD)	3.02	pH 8	(1) ACD
logD (LOGD)	3.28	pH 10	(1) ACD
logP (LOGP)	3.282+/-0.692		(1) ACD
Molar Solubility (SLB.MOL)	>=0.01 - <0.1 mol/L	pH 1	(1) ACD
Molar Solubility (SLB.MOL)	>=0.01 - <0.1 mol/L	pH 4	(1) ACD
Molar Solubility (SLB.MOL)	<0.01 mol/L	pH 7	(1) ACD
Molar Solubility (SLB.MOL)	<0.01 mol/L	pH 8	(1) ACD
Molar Solubility (SLB.MOL)	<0.01 mol/L	pH 10	(1) ACD
Molecular Weight (MW)	550.69		(1) ACD
pKa (PKA)	7.77+/-0.25	Most Basic	(1) ACD
Vapor Pressure (VP)	3.07E-20 Torr	25.0 deg C	(1) ACD

(1) Calculated using Advanced Chemistry Development (ACD) Software Solaris V4.67 ((C) 1994-2003 ACD)

3 REFERENCES IN FILE CA (1957 TO DATE)
3 REFERENCES IN FILE CAPLUS (1957 TO DATE)

REFERENCE 1

AN 136:325823 CA
TI Preparation and formulation of proline derivatives as mediators of hedgehog signaling pathways for pharmaceutical and cosmetic uses
IN Baxter, Anthony D.; Boyd, Edward A.; Guicherit, Oivin M.; Price, Stephen; Rubin, Lee D.
PA Curis, Inc., USA
SO PCT Int. Appl., 230 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-40
ICS A61K031-495; A61K009-08
CC 34-2 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 62, 63
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002030421	A2	20020418	WO 2001-US32054	20011012
	WO 2002030421	A3	20020926		
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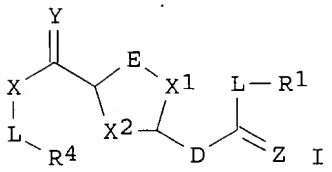
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 6552016	B1	20030422	US 2000-688018	20001013
	AU 2002011713	A5	20020422	AU 2002-11713	20011012
	US 2002165221	A1	20021107	US 2001-977096	20011012

PRAI US 2000-240536P 20001013
US 1999-159417P 19991014
US 2000-196543P 20000411
US 2000-211919P 20000616
US 2000-240564P 20001013
WO 2001-US32054 20011012

GI



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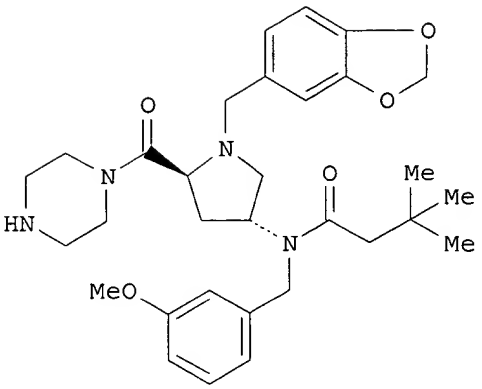

II

AB Proline-based compds. such as I [R1, R4 = H, alkyl, (CH2)n-(hetero)aryl (n = 0-5); L = null, -(CH2)n-, -alkenyl-, -alkynyl-, -(CH2)n-alkenyl-, -(CH2)n-alkynyl-, -(CH2)nO(CH2)p-, -(CH2)nNR8(CH2)p-, -(CH2)nS(CH2)p-, -(CH2)nalkenyl(CH2)p-, -(CH2)nalkynyl(CH2)p-, -O(CH2)n-,-NR8(CH2)n-, or -S(CH2)n- (R8 is any group given for R1 or two R8 together may form a 4- to 8-membered ring; p = 0-3); X, D = NR8, O, S, NR8NR8, ONR8, or a direct bond; Y, Z = O or S; E represents NR5, where R5 represents LR8 or an ammonium salt; X1, X2 = null, CH2 or CH2CH2] were prepd. for pharmaceutical and cosmetic use. Thus, proline deriv. II was prepd. via a multistep synthetic sequence which started with trans-4-hydroxy-L-proline, 3-methoxybenzaldehyde, piperonal, tert-butylacetyl chloride, and N-(tert-butoxycarbonyl)piperazine. The prepd. proline derivs. were tested for agonist activity for inhibiting aberrant growth states resulting from hedgehog gain-of-function, ptc loss-of-function or smoothened gain-of-function comprising contacting the cell with a hedgehog antagonist, such as a small mol., in a sufficient amt. to aberrant growth state, e.g., to agonize a normal ptc pathway or antagonize smoothened or hedgehog activity.

ST proline deriv prepn hedgehog signaling pathway mediator; cosmetic proline deriv prepn hedgehog signaling pathway mediator; basal cell carcinoma preventative proline deriv prepn; spermatogenesis regulator proline deriv prepn; hematopoiesis regulator proline deriv prepn

IT Skin, neoplasm
(basal cell carcinoma, preventative; prepn. and formulation of proline derivs. for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

IT Cosmetics
(prepn. and formulation of proline derivs. for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

IT Hematopoiesis
Spermatogenesis
(regulators; prepn. and formulation of proline derivs. for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

IT Hedgehog protein
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(sonic; prepn. and formulation of proline derivs. for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

IT 334999-41-6P 334999-57-4P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. and formulation of proline derivs. for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

IT 334998-24-2P 334998-25-3P 334998-26-4P 334998-27-5P 334998-28-6P 334998-29-7P 334998-30-0P 334998-31-1P 334998-32-2P 334998-33-3P

334998-34-4P 334998-35-5P 334998-36-6P 334998-37-7P 334998-38-8P
334998-39-9P 334998-40-2P 334998-41-3P 334998-42-4P 334998-43-5P
334998-44-6P 334998-45-7P 334998-46-8P 334998-47-9P 334998-48-0P
334998-49-1P 334998-50-4P 334998-51-5P 334998-52-6P 334998-53-7P
334998-54-8P 334998-55-9P 334998-56-0P 334998-57-1P 334998-58-2P
334998-59-3P 334998-60-6P 334998-61-7P 334998-62-8P 334998-63-9P
334998-64-0P 334998-65-1P 334998-66-2P 334998-67-3P 334998-68-4P
334998-69-5P 334998-70-8P 334998-71-9P 334998-72-0P 334998-73-1P
334998-74-2P 334998-75-3P 334998-76-4P 334998-77-5P 334998-78-6P
334998-79-7P 334998-80-0P 334998-81-1P 334998-82-2P 334998-83-3P
334998-84-4P 334998-85-5P 334998-86-6P 334998-87-7P 334998-88-8P
334998-89-9P 334998-90-2P 334998-91-3P 334998-92-4P 334998-93-5P
334998-94-6P 334998-95-7P 334998-96-8P 334998-97-9P 334998-98-0P
334998-99-1P 334999-00-7P 334999-03-0P 334999-05-2P 334999-07-4P
334999-09-6P 334999-11-0P 334999-13-2P 334999-15-4P 334999-17-6P
334999-19-8P 334999-21-2P 334999-24-5P 334999-94-9P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and formulation of proline derivs. for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

IT 51-35-4 591-31-1 623-05-2 7065-46-5 7693-46-1 57260-71-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. and formulation of proline derivs. for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

IT 623-05-2DP, polymer bound 40216-83-9P 74844-91-0P 84520-67-2P
84520-68-3P 121147-97-5P 121148-01-4P 334999-29-0P 334999-32-5P
334999-33-6P 334999-34-7P 334999-35-8P 334999-36-9P 334999-37-0P
334999-38-1P 334999-39-2P 334999-43-8P 334999-45-0P 334999-47-2P
334999-48-3P 334999-51-8P 334999-53-0P 334999-55-2P 334999-60-9DP, polymer bound
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and formulation of proline derivs. for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

REFERENCE 2

AN 136:304056 CA
TI Hedgehog antagonists, methods and uses related thereto
IN Dudek, Henryk; Pepicelli, Carmen; Karavanov, Irina
PA Curis, Inc., USA
SO PCT Int. Appl., 224 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K039-395
CC 1-6 (Pharmacology)
Section cross-reference(s): 9, 14
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002030462	A2	20020418	WO 2001-US32100	20011015
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2002165221	A1	20021107	US 2001-977096	20011012
	AU 2001096844	A5	20020422	AU 2001-96844	20011015

PRAI US 2000-240564P 20001013
US 2000-240536P 20001013
WO 2001-US32100 20011015

AB The present application is directed to compns. and methods for inhibiting angiogenesis and treating or preventing unwanted cell proliferation, including tumors, by inhibiting the hedgehog pathway, e.g., with an antagonist of the hedgehog pathway such as those disclosed herein. In one embodiment, the subject methods may be used to inhibit unwanted cell proliferation by detg. whether cells overexpress a gli gene, and contacting cells that overexpress gli gene with an effective amt. of a hedgehog antagonist. In preferred embodiments ,the unwanted cell proliferation is cancer or benign prostatic hyperplasia. Another aspect of the present invention involves measuring the levels of gli gene expression in order detn. the likelihood that a cancer will develop or to detn. a cancer treatment protocol. Another embodiment of the invention involves methods for using hedgehog antagonists to stimulate surfactant prodn. or lamellated body formation in lung cells, esp. the lung cells of premature infants. In other preferred embodiments, hedgehog antagonists are selected from small mols., hedgehog antibodies, antisense nucleic acids and ribozymes.

ST hedgehog pathway antagonist antiproliferative agent gli gene; lung surfactant prodn hedgehog pathway antagonist

IT Lung, neoplasm
(adenocarcinoma, alveolar; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Prostate gland
(adenocarcinoma, inhibitors; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Antitumor agents
(adenocarcinoma; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Prostate gland
(benign hyperplasia, inhibition; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Antitumor agents
(bladder carcinoma; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Antitumor agents
(bronchi carcinoma, adenocarcinoma; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Diagnosis
(cancer; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Bronchi
(carcinoma, inhibitors, adenocarcinoma; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Bladder
Mammary gland
(carcinoma, inhibitors; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Intestine, neoplasm

(colon, inhibitors; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Antitumor agents
(colon; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Neoplasm
(diagnosis; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Antitumor agents
(genitourinary tract tumor inhibitors; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gli-1; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gli; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Antitumor agents
Cytotoxic agents
Drug screening
High throughput screening
Human
Signal transduction, biological
Surfactants
(hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Hedgehog protein
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Antisense oligonucleotides
Ribozymes
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Embryo, animal
(hedgehog signaling pathway in maturation of; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Lung, neoplasm
Neoplasm
(hedgehog signaling pathway in; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Lung, neoplasm
(inhibitors; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Lung

(lamellated body formation and surfactant prodn. in; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Antitumor agents
(lung small-cell carcinoma; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Antitumor agents
(lung; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Antitumor agents
(mammary gland carcinoma; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Antitumor agents
(mammary gland; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Bladder
Mammary gland
Prostate gland
(neoplasm, hedgehog signaling pathway in; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Mammary gland
Prostate gland
(neoplasm, inhibitors; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Mutation
(of hedgehog protein; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Newborn
(premature; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Antitumor agents
(prostate adenocarcinoma; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Antitumor agents
(prostate gland; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Lung, neoplasm
(small-cell carcinoma, inhibitors; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Hedgehog protein
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(sonic; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Antibodies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(to hedgehog protein; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Urogenital tract
(tumor inhibitors; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT 77-59-8, Tomatidine 78-41-1, Triparanol 366-93-8, AY9944 469-59-0, Jervine 4449-51-8, Cyclopamine 330796-27-5 334998-27-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

REFERENCE 3

AN 134:311102 CA
TI Preparation and formulation of heterocycles as mediators of hedgehog signaling pathways for pharmaceutical and cosmetic uses
IN Baxter, Anthony David; Boyd, Edward Andrew; Guicherit, Oivin M.; Price, Stephen; Rubin, Lee
PA Curis, Inc., USA
SO PCT Int. Appl., 219 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-00
CC 27-10 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 62, 63
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001026644	A2	20010419	WO 2000-US28579	20001013
	WO 2001026644	A3	20020418		
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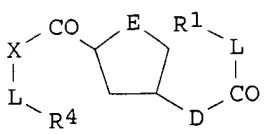
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	EP 1227805	A2	20020807	EP 2000-978225	20001013
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
	JP 2003511411	T2	20030325	JP 2001-529434	20001013
	US 6552016	B1	20030422	US 2000-688018	20001013

PRAI US 1999-159417P 19991014
US 2000-196543P 20000411
US 2000-211919P 20000616
US 2000-240536P 20001013
WO 2000-US28579 20001013

GI



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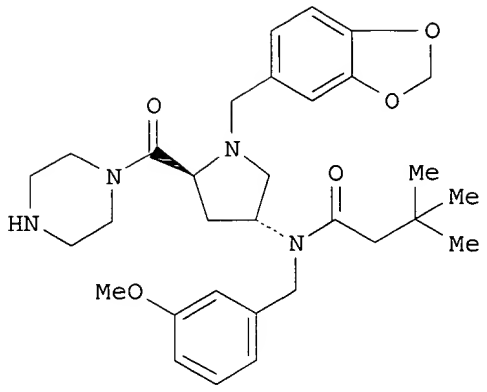

II

AB Heterocycles, such as I [E = O, S, NR; D, X = NR2, O, S, bond, etc.; L = linking group, such as alkylene, alkenylene, alkynylene; XL = piperazin-1,4-diyl, etc.; R, R1, R2 = H, alkyl, acyl, arylalkyl, heteroarylalkyl, etc.], were prepd. for pharmaceutical and cosmetic use. Thus, pyrrolidine II was prepd. via a multistep synthetic sequence which started with trans-4-hydroxy-L-proline, 3-methoxybenzaldehyde, piperonal, tert-butylacetyl chloride, and N-(tert-butoxycarbonyl)piperazine. The prepd. pyrrolidines were tested for agonist activity for inhibiting aberrant growth states resulting from hedgehog gain-of-function, ptc loss-of-function or smoothened gain-of-function comprising contacting the cell with a hedgehog antagonist, such as a small mol., in a sufficient amt. to aberrant growth state, e.g., to agonize a normal ptc pathway or antagonize smoothened or hedgehog activity.

ST pyrrolidine prepn hedgehog signaling pathway mediator; cosmetic pyrrolidine prepn hedgehog signaling pathway mediator; basal cell carcinoma preventative pyrrolidine prepn; spermatogenesis regulator pyrrolidine prepn; hematopoiesis regulator pyrrolidine prepn

IT Skin, neoplasm
(basal cell carcinoma, preventative; prepn. and formulation of pyrrolidines for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

IT Cosmetics
(prepn. and formulation of pyrrolidines for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

IT Hematopoiesis
Spermatogenesis
(regulators; prepn. and formulation of pyrrolidines for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

IT Hedgehog protein
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(sonic; prepn. and formulation of pyrrolidines for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

IT 334999-41-6P 334999-57-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. and formulation of pyrrolidines for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

IT 334998-24-2P 334998-25-3P 334998-26-4P 334998-27-5P 334998-28-6P
334998-29-7P 334998-30-0P 334998-31-1P 334998-32-2P 334998-33-3P
334998-34-4P 334998-35-5P 334998-36-6P 334998-37-7P 334998-38-8P
334998-39-9P 334998-40-2P 334998-41-3P 334998-42-4P 334998-43-5P
334998-44-6P 334998-45-7P 334998-46-8P 334998-47-9P 334998-48-0P
334998-49-1P 334998-50-4P 334998-51-5P 334998-52-6P 334998-53-7P
334998-54-8P 334998-55-9P 334998-56-0P 334998-57-1P 334998-58-2P

334998-59-3P 334998-60-6P 334998-61-7P 334998-62-8P 334998-63-9P
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334998-69-5P 334998-70-8P 334998-71-9P 334998-72-0P 334998-73-1P
334998-74-2P 334998-75-3P 334998-76-4P 334998-77-5P 334998-78-6P
334998-79-7P 334998-80-0P 334998-81-1P 334998-82-2P 334998-83-3P
334998-84-4P 334998-85-5P 334998-86-6P 334998-87-7P 334998-88-8P
334998-89-9P 334998-90-2P 334998-91-3P 334998-92-4P 334998-93-5P
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334999-09-6P 334999-11-0P 334999-13-2P 334999-15-4P 334999-17-6P
334999-19-8P 334999-21-2P 334999-24-5P 334999-94-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and formulation of pyrrolidines for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

IT 51-35-4 591-31-1 623-05-2 7065-46-5 7693-46-1 57260-71-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. and formulation of pyrrolidines for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

IT 623-05-2DP, polymer bound 40216-83-9P 74844-91-0P 84520-67-2P
84520-68-3P 121147-97-5P 121148-01-4P 334999-29-0P 334999-32-5P
334999-33-6P 334999-34-7P 334999-35-8P 334999-36-9P 334999-37-0P
334999-38-1P 334999-39-2P 334999-43-8P 334999-45-0P 334999-47-2P
334999-48-3P 334999-51-8P 334999-53-0P 334999-55-2P 334999-60-9DP, polymer bound
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and formulation of pyrrolidines for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

=>

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L1             0 S 334998027-5/CN
L2             0 S 334998027-5
L3             1 S 334998-27-5

     FILE 'REGISTRY' ENTERED AT 13:39:08 ON 08 MAY 2003

     FILE 'CAPLUS' ENTERED AT 13:39:11 ON 08 MAY 2003

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L4             2 L3/PREP
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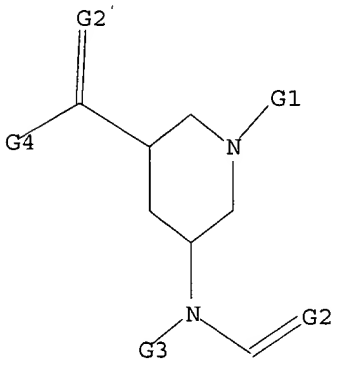
L1 HAS NO ANSWERS
L1 STR



G1 C,S

G2 O,S

G3 H,S,N

G4 C,H,O,S,N

Structure attributes must be viewed using STN Express query preparation.

=> s l1 sss full
FULL SEARCH INITIATED 14:07:42
FULL SCREEN SEARCH COMPLETED - 142 TO ITERATE

100.0% PROCESSED 142 ITERATIONS 40 ANSWERS
SEARCH TIME: 00.00.01

L2 40 SEA SSS FUL L1

=> d 1-40

L2 ANSWER 1 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 471895-15-5 REGISTRY
CN 1,3-Piperidinedicarboxylic acid, 5-[[[3-(2-chloro-6-fluorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-, 1-(1,1-dimethylethyl) 3-ethyl ester, (3R,5S)-rel- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C24 H29 Cl F N3 O6
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Relative stereochemistry.

or treatment of premature infants)

ACCESSION NUMBER: 2002:295175 USPATFULL

TITLE: Mediators of hedgehog signaling pathways, compositions and uses related thereto

INVENTOR(S): Baxter, Anthony David, Hertfordshire, UNITED KINGDOM
Boyd, Edward Andrew, Oxfordshire, UNITED KINGDOM
Guicherit, Oivin M., Belmont, MA, UNITED STATES
Price, Stephen, Buckinghamshire, UNITED KINGDOM
Rubin, Lee L., Wellesley, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002165221	A1	20021107
APPLICATION INFO.:	US 2001-977096	A1	20011012 (9)

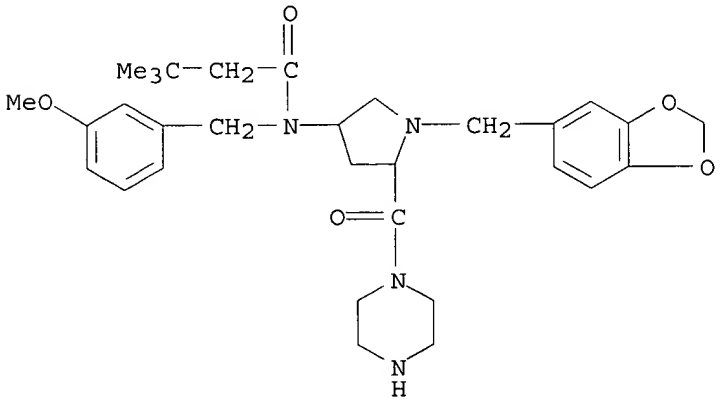
	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-240536P	20001013 (60)
	US 2000-240564P	20001013 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: ROPES & GRAY, ONE INTERNATIONAL PLACE, BOSTON, MA, 02110-2624
NUMBER OF CLAIMS: 92
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 58 Drawing Page(s)
LINE COUNT: 5140
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **334998-27-5**
(hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

RN 334998-27-5 USPATFULL

CN Butanamide, N-[1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl- (9CI) (CA INDEX NAME)



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L5              0 S L3 AND L4
L6              2 S US2002165221/PN
L7              0 S L3 AND L6
L8              2 S US2002165221/PN
L9              0 S L3 AND L8
L10            13 S L2

     FILE 'USPATFULL' ENTERED AT 14:30:42 ON 08 MAY 2003

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L11             3 L2

=> d 1-3 hit, ibib, hitstr
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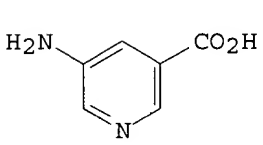
L10 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2003 ACS
AN 1982:104706 CAPLUS
DN 96:104706
TI Syntheses of some aminopiperidinecarboxylic acids related to nipecotic acid
AU Jacobsen, Poul; Schaumburg, Kjeld; Larsen, Jens Joergen; Krogsgaard-Larsen, Povl
CS Dep. Chem. BC, R. Danish Sch. Pharm., Copenhagen, DK-2100, Den.
SO Acta Chemica Scandinavica, Series B: Organic Chemistry and Biochemistry (1981), B35(4), 289-94
CODEN: ACBOCV; ISSN: 0302-4369
DT Journal
LA English
CC 34-2 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 27
GI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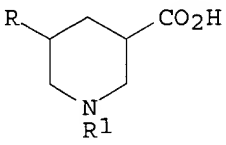
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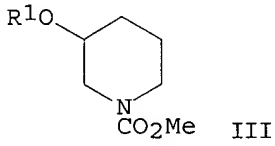
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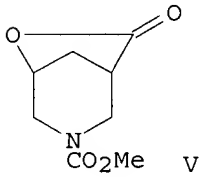
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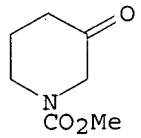
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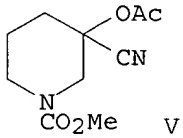
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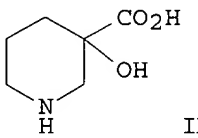
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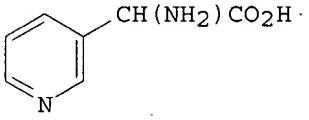
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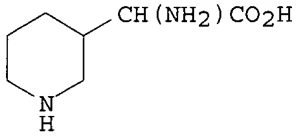
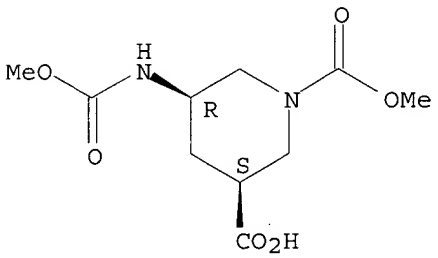

XI

AB The hydrogenation of 5-aminonicotinic acid (I) over PtO2 gave a complex mixt., which was treated with ClCO2Me to give piperidinecarboxylates (3RS,5SR)-II (R = OH, NHCO2Me; R1 = CO2Me) and an inseparable mixt. of piperidinecarboxylate (RS)-III (R1 = H) (IV) and lactone (3RS,5SR)-V. Acetylation of the latter mixt. converted IV to (RS)-III (R1 = Ac), which was sepd. from (3RS,5SR)-V by column chromatog. (3RS,5SR)-II (R = OH, R1 = CO2Me) was cleaved by 48% HBr to give (3RS,5SR)-II.HBr (R = OH, R1 = H), whereas (3RS,5SR)-II (R = NHCO2Me, R1 = CO2Me) was cleaved by 6M HCl to give (3RS,5SR)-II.HCl (R = NH2, R1 = H) (VI). The hydrogenation of I over Rh-Al2O3 gave VI. Piperidinone VII was treated with KCN/AcOH to give piperidinenitrile (RS)-VIII, which was cleaved and hydrolyzed by 48% HBr to give piperidinecarboxylate (RS)-IX.HBr. Pyridylglycine (RS)-X.HBr and piperidylglycine (RS)-XI.HBr were also prepd.
ST aminopiperidinecarboxylic acid; piperidinecarboxylic acid amino; nipecotic acid
IT 20826-04-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(amination of)
IT 61995-18-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(hydrogenation of)

IT 80613-04-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and acetylation of)
IT 80613-06-5P **80613-07-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and cleavage of)
IT 24242-19-1P 80613-13-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and hydrogenation of)
IT 80613-11-2P 80613-14-5P 80613-15-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and hydrolysis of)
IT 80613-05-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and ring cleavage of)
IT 498-95-3DP, derivs. 80613-08-7P 80613-09-8P 80613-10-1P
80613-12-3P 80613-16-7P 80613-17-8P 80613-18-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)
IT 39931-77-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with ammonia)
IT **80613-07-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and cleavage of)
RN 80613-07-6 CAPLUS
CN 1,3-Piperidinedicarboxylic acid, 5-[(methoxycarbonyl)amino]-, 1-methyl ester, cis- (9CI) (CA INDEX NAME)

Relative stereochemistry.



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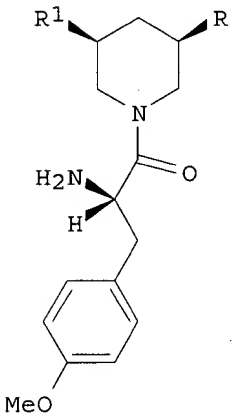
L10 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2003 ACS
AN 1995:109473 CAPLUS
DN 122:240300
TI Heterocyclic analogs of nucleosides: synthesis and biological evaluation of novel analogs of puromycin
AU Hultin, Philip G.; Szarek, Walter A.
CS Dep. Chem., Queen's Univ., Kingston, ON, K7L 3N6, Can.
SO Canadian Journal of Chemistry (1994), 72(9), 1978-89
CODEN: CJCHAG; ISSN: 0008-4042
DT Journal
LA English
CC 33-9 (Carbohydrates)
Section cross-reference(s): 1, 22
GI



I

AB The diastereomeric 1-(piperidine-3'-yl)uracil compds. and the N6-dimethyl-9-(piperidine-3'-yl)adenine compds. I (R = CH2OH, R1 = uracil, N6-dimethyladenine; R = uracil, N6-dimethyladenine, R1 = CH2OH) have been prepd. as analogs of the naturally occurring aminoacyl nucleoside antibiotic puromycin. The diastereomers were sepd. using HPLC, and the abs. configuration of I were assigned. These puromycin analogs have been tested for anti-HIV and antitumor activity in vitro.

ST puromycin analog prepn virucide antitumor; abs configuration puromycin analog; piperidineyluracil prepn virucide antitumor; piperidineyladenine prepn virucide antitumor

IT Nucleosides, preparation
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(piperidineyluracils and piperidineyladenines; synthesis and antitumor and antiviral activities of puromycin analogs)

IT Neoplasm inhibitors
Virucides and Virustats
(synthesis and antitumor and antiviral activities of puromycin analogs)

IT Configuration
(abs., synthesis and antitumor and antiviral activities of puromycin analogs)

IT 53-79-2DP, Puromycin, analogs 162315-06-2P 162427-36-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis and antitumor and antiviral activities of puromycin analogs)

IT 162315-07-3P 162427-37-4P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis and antitumor and antiviral activities of puromycin analogs)

IT 53267-93-9 57796-78-8 61865-48-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis and antitumor and antiviral activities of puromycin analogs)

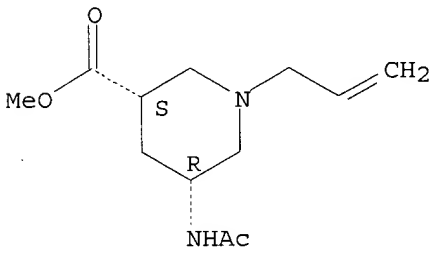
IT 162314-91-2P 162314-92-3P 162314-94-5P 162314-95-6P 162314-96-7P
162314-97-8P 162314-98-9P 162314-99-0P 162315-00-6P 162315-01-7P
162315-02-8P 162315-03-9P 162315-04-0P 162315-05-1P 162341-49-3P
162427-34-1P 162427-35-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and antitumor and antiviral activities of puromycin analogs)

IT **162314-93-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis and antitumor and antiviral activities of puromycin analogs)

IT **162314-93-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis and antitumor and antiviral activities of puromycin analogs)

RN 162314-93-4 CAPLUS
CN 3-Piperidinecarboxylic acid, 5-(acetylamino)-1-(2-propenyl)-, methyl ester, cis- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L10 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2003 ACS
AN 1995:826481 CAPLUS
DN 123:227980
TI Preparation of 3-amino-5-carboxypiperidine and 3-amino-4-carboxypyrrolidine tachykinin antagonists
IN Ikunaka, Masaya; Shishido, Yuuji; Nakane, Masami
PA Pfizer Inc., USA; Pfizer Pharmaceuticals Inc.
SO PCT Int. Appl., 72 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07D207-16
ICS C07D211-60; A61K031-40; A61K031-445
CC 27-10 (Heterocyclic Compounds (One Hetero Atom))
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9507886	A1	19950323	WO 1994-JP1514	19940913
	W: CA, FI, JP, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2171637	AA	19950323	CA 1994-2171637	19940913
	EP 719253	A1	19960703	EP 1994-926394	19940913
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	JP 10509414	T2	19980914	JP 1994-509087	19940913
	JP 2992346	B2	19991220		
	FI 9601239	A	19960315	FI 1996-1239	19960315
	US 6083943	A	20000704	US 1999-280403	19990319
PRAI	JP 1993-255064	A	19930917		
	WO 1994-JP1514	W	19940913		
	US 1997-957176	B1	19971024		

OS MARPAT 123:227980
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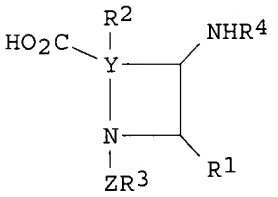

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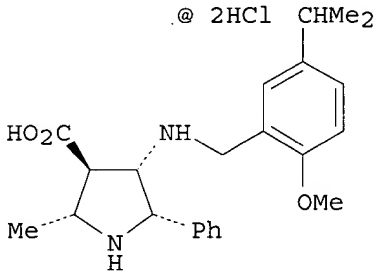


II

AB The title compds. [I; R1 = (un)substituted Ph, biphenyl, indolyl, naphthyl, thienyl, furyl, pyridyl, etc.; R2 = H, C1-6 alkyl; R3 = H, CN, OH, NH2, CO2H; R4 = (un)substituted PhCH2, (un)substituted heterocyclyl; Y = C2-4 alkylene; Z = direct bond, C1-6 alkylene], useful as tachykinin antagonists (no data) for the treatment of gastrointestinal (no data) and CNS disorders (no data), are prepd. Thus, (2S,3S,4S,5R)-4-carboxy-3-[N-(5-isopropyl-2-methoxybenzyl)amino]-5-methyl-2-phenylpyrrolidine dihydrochloride, II, was prepd. in 27 steps from PhCHO.
ST aminocarboxypyrrolidine tachykinin antagonist; aminocarboxypiperidine tachykinin antagonist
IT Allergy inhibitors
Analgesics
Antiemetics
Inflammation inhibitors
(3-amino-5-carboxypiperidines and 3-amino-4-carboxypyrrolidines)
IT Bronchodilators

(antiasthmatics, 3-amino-5-carboxypiperidines and 3-amino-4-carboxypyrrolidines)

IT Nervous system
(central, disease, 3-amino-5-carboxypiperidine and 3-amino-4-carboxypyrrolidine tachykinin antagonists for treatment of)

IT Digestive tract
(disease, 3-amino-5-carboxypiperidine and 3-amino-4-carboxypyrrolidine tachykinin antagonists for treatment of)

IT Headache
(migraine, 3-amino-5-carboxypiperidine and 3-amino-4-carboxypyrrolidine tachykinin antagonists for treatment of)

IT Kinins (animal hormones)
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(tachykinins, prepn. of 3-amino-5-carboxypiperidine and 3-amino-4-carboxypyrrolidine tachykinin antagonists from)

IT 168321-02-6
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(claimed compd.; prepn. of 3-amino-5-carboxypiperidine and 3-amino-4-carboxypyrrolidine tachykinin antagonists)

IT 168320-98-7P 168320-99-8P 168321-01-5P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 3-amino-5-carboxypiperidine and 3-amino-4-carboxypyrrolidine tachykinin antagonists)

IT 75-24-1, Trimethylaluminum 75-65-0, tert-Butanol, reactions 100-52-7, Benzaldehyde, reactions 501-53-1, Benzyl chloroformate 3513-81-3, 2-Methylene-1,3-propanediol 5680-79-5, Glycine methyl ester hydrochloride 18162-48-6, tert-Butyldimethylsilyl chloride 24424-99-5, Di-tert-butyl dicarbonate 85902-68-7, 5-Isopropyl-2-methoxybenzaldehyde 96746-23-5 145742-65-0, 2-Methoxy-5-trifluoromethoxybenzaldehyde 151101-22-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of 3-amino-5-carboxypiperidine and 3-amino-4-carboxypyrrolidine tachykinin antagonists from)

IT 66646-88-6P, N-Benzylidene glycine methyl ester 168321-00-4P
168321-03-7P 168321-04-8P 168321-05-9P 168321-06-0P 168321-07-1P
168321-08-2P 168321-09-3P 168321-10-6P 168321-11-7P 168321-12-8P
168321-13-9P 168321-14-0P 168321-15-1P 168321-16-2P 168321-17-3P
168321-18-4P 168321-19-5P 168321-20-8P 168321-21-9P 168321-22-0P
168321-23-1P 168321-24-2P 168321-25-3P 168321-26-4P 168321-27-5P
168321-28-6P 168321-29-7P 168321-30-0P 168321-31-1P 168321-32-2P
168321-33-3P 168321-34-4P 168321-35-5P 168321-36-6P 168321-37-7P
168321-38-8P 168321-39-9P 168321-40-2P **168321-41-3P**
168321-42-4P 168321-43-5P 168321-44-6P 168321-45-7P
168321-46-8P 168321-47-9P 168321-48-0P 168321-49-1P 168321-50-4P
168321-51-5P 168321-52-6P 168321-53-7P 168321-54-8P 168321-55-9P
168321-56-0P 168321-57-1P 168321-58-2P 168321-59-3P
168321-60-6P 168321-61-7P 168321-62-8P 168321-63-9P 168321-64-0P
168321-65-1P 168321-66-2P 168321-67-3P 168321-68-4P 168608-19-3P
168608-20-6P 168608-21-7P 168608-22-8P 168608-23-9P 168608-24-0P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 3-amino-5-carboxypiperidine and 3-amino-4-carboxypyrrolidine tachykinin antagonists from)

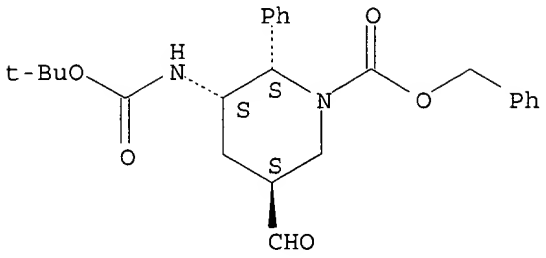
IT **168321-41-3P 168321-42-4P 168321-56-0P 168321-57-1P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 3-amino-5-carboxypiperidine and 3-amino-4-carboxypyrrolidine tachykinin antagonists from)

RN 168321-41-3 CAPLUS

CN 1-Piperidinecarboxylic acid, 3-[[(1,1-dimethylethoxy)carbonyl]amino]-5-formyl-2-phenyl-, phenylmethyl ester, (2.alpha.,3.alpha.,5.beta.)- (9CI)

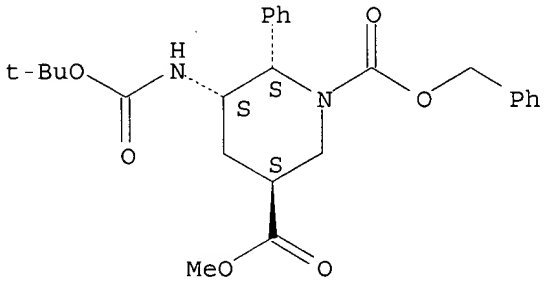
(CA INDEX NAME)

Relative stereochemistry.



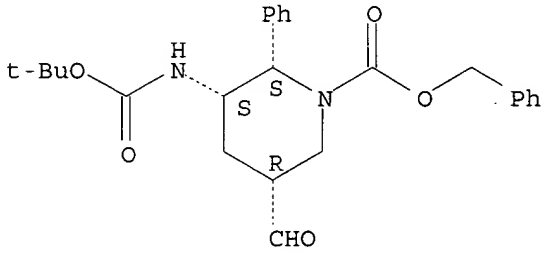
RN 168321-42-4 CAPLUS
CN 1,3-Piperidinedicarboxylic acid, 5-[[(1,1-dimethylethoxy)carbonyl]amino]-6-phenyl-, 3-methyl 1-(phenylmethyl) ester, (3.alpha.,5.beta.,6.beta.)- (9CI) (CA INDEX NAME)

Relative stereochemistry.



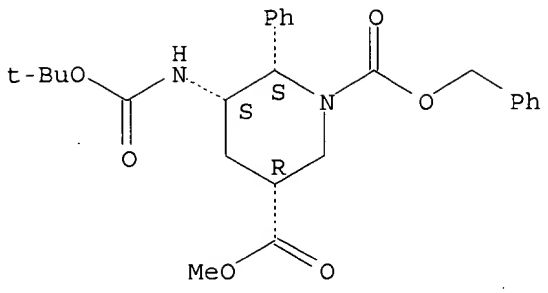
RN 168321-56-0 CAPLUS
CN 1-Piperidinecarboxylic acid, 3-[[(1,1-dimethylethoxy)carbonyl]amino]-5-formyl-2-phenyl-, phenylmethyl ester, (2.alpha.,3.alpha.,5.alpha.)- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 168321-57-1 CAPLUS
CN 1,3-Piperidinedicarboxylic acid, 5-[[(1,1-dimethylethoxy)carbonyl]amino]-6-phenyl-, 3-methyl 1-(phenylmethyl) ester, (3.alpha.,5.alpha.,6.alpha.)- (9CI) (CA INDEX NAME)

Relative stereochemistry.


Ph
O
H
N
t-BuO
S
S
N
O
Ph
O
R
MeO
O

L10 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2003 ACS
AN 1997:453941 CAPLUS
DN 127:65769
TI Preparation of imidazolyl-substituted piperidines as inhibitors of farnesyl-protein transferase
IN Kim, Byeong M.; Shaw, Anthony W.; Graham, Samuel L.; Desolms, S. Jane; Ciccarone, Terrence M.
PA Merck and Co., Inc., USA; Kim, Byeong M.; Shaw, Anthony W.; Graham, Samuel L.; Desolms, S. Jane; Ciccarone, Terrence M.
SO PCT Int. Appl., 197 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-445
ICS C07D401-12
CC 28-9 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9718813	A1	19970529	WO 1996-US18811	19961118
	W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	CA 2238081	AA	19970529	CA 1996-2238081	19961118
	AU 9711626	A1	19970611	AU 1997-11626	19961118
	AU 704139	B2	19990415		
	EP 862435	A1	19980909	EP 1996-942798	19961118
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
	JP 2000500502	T2	20000118	JP 1997-519941	19961118
PRAI	US 1995-7498P	P	19951122		
	GB 1996-4311	A	19960229		
	WO 1996-US18811	W	19961118		

OS MARPAT 127:65769
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title compds. [I; R1a, R1b, R1c = H, (un)substituted aryl, heteroaryl, etc.; R2 = H, (un)substituted C1-8 alkyl, aryl, etc.; R3 = H, C(O)NR6R7 (wherein R6, R7 = H, C1-4 alkyl, C3-6 cycloalkyl, etc.), C(O)OR6; R4 = H, (un)substituted aryl, heteroaryl, etc.; R5 = H, C2-6 alkenyl, C2-6 alkynyl, etc.; A1, A2 = a bond, CH:CH, C.tplbond.C, etc.; V = H, heterocycle, aryl, etc.; W = heterocycle; X = a bond, C(O)NH, NHC(O), etc.; n, p, q = 0-4; r = 0-5 (r = 0 when V = H); s = 1-2; t = 0-1] and their salts which inhibit farnesyl-protein transferase (FPTase) and the farnesylation of the oncogene protein Ras, and useful in treating cancer, neurofibromin benign proliferative disorder, blindness, infections from hepatitis delta and related viruses, polycystic kidney disease, and in preventing restenosis, were prepd. Thus, reaction of 1-tert-butoxycarbonyl-cis-3-methoxycarbonyl-piperidine-5-carboxylic acid with 3-(4-cyanobenzyl)histamine in the presence of HOBT, EDC and Et3N in DMF followed by treatment of the resulting 1-tert-butoxycarbonyl-cis-3-methoxycarbonyl-5-{N-[1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl]carbamoyl}piperidine with CF3COOH in CH2Cl2, and reaction of the deprotected intermediate with phenylacetaldehyde in the presence of

NaBH3CN in MeOH afforded the title compd. II which showed IC50 of < 10 .mu.M against human FPTase.

ST farnesyl protein transferase inhibitor piperidine prepn; farnesylation Ras oncogene protein piperidine prepn; anticancer agent imidazolyl piperidine prepn; neurofibromin benign proliferative disorder piperidine prepn; blindness imidazolyl piperidine prepn; antiviral agent hepatitis delta piperidine prepn; restenosis piperidine prepn; polycystic kidney disease piperidine prepn

IT Artery, disease
(coronary, restenosis, treatment of; prepn. of imidazolyl-substituted piperidines as inhibitors of farnesyl-protein transferase)

IT Kidney, disease
(polycystic, treatment of; prepn. of imidazolyl-substituted piperidines as inhibitors of farnesyl-protein transferase)

IT Antitumor agents
(prepn. of imidazolyl-substituted piperidines as inhibitors of farnesyl-protein transferase)

IT Disease, animal
(proliferative, treatment of neurofibromin benign proliferative disorder; prepn. of imidazolyl-substituted piperidines as inhibitors of farnesyl-protein transferase)

IT Antiviral agents
(treatment of infections from hepatitis delta and related viruses; prepn. of imidazolyl-substituted piperidines as inhibitors of farnesyl-protein transferase)

IT Neurofibromin
RL: MSC (Miscellaneous)
(treatment of neurofibromin benign proliferative disorder; prepn. of imidazolyl-substituted piperidines as inhibitors of farnesyl-protein transferase)

IT Blindness
(treatment of; prepn. of imidazolyl-substituted piperidines as inhibitors of farnesyl-protein transferase)

IT 191543-37-0P 191543-38-1P 191543-39-2P 191543-57-4P
191543-60-9P 191543-79-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of imidazolyl-substituted piperidines as inhibitors of farnesyl-protein transferase)

IT 191543-40-5P 191543-41-6P 191543-42-7P 191543-43-8P 191543-44-9P
191543-45-0P 191543-46-1P 191543-47-2P 191543-48-3P 191543-49-4P
191543-50-7P 191543-51-8P 191543-52-9P 191543-53-0P 191543-54-1P
191543-55-2P 191543-56-3P 191543-58-5P 191543-59-6P
191543-62-1P 191543-64-3P 191543-66-5P 191543-68-7P
191543-70-1P 191543-72-3P 191543-74-5P 191543-76-7P 191543-77-8P
191543-81-4P 191543-83-6P 191543-85-8P 191543-87-0P 191543-89-2P
191543-91-6P 191543-92-7P 191543-93-8P 191543-94-9P 191543-95-0P
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191544-06-6P 191544-07-7P 191544-08-8P 191544-09-9P 191544-10-2P
191544-11-3P 191544-12-4P 191544-13-5P 191544-14-6P 191544-15-7P
191544-16-8P 191544-17-9P 191544-18-0P 191544-19-1P 191544-20-4P
191544-21-5P 191544-23-7P 191544-24-8P 191544-25-9P 191544-26-0P
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191544-37-3P 191544-39-5P 191544-40-8P 191544-41-9P 191544-42-0P
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191544-48-6P 191544-49-7P 191544-50-0P 191544-51-1P 191544-53-3P
191544-55-5P 191544-56-6P 191544-57-7P 191544-58-8P 191544-59-9P
191544-60-2P 191544-61-3P 191544-62-4P 191544-63-5P 191544-64-6P
191544-65-7P 191544-66-8P 191544-67-9P 191544-68-0P 191544-69-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of imidazolyl-substituted piperidines as inhibitors of farnesyl-protein transferase)

IT 131384-38-8, Farnesyl-protein transferase
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(prepn. of imidazolyl-substituted piperidines as inhibitors of farnesyl-protein transferase)

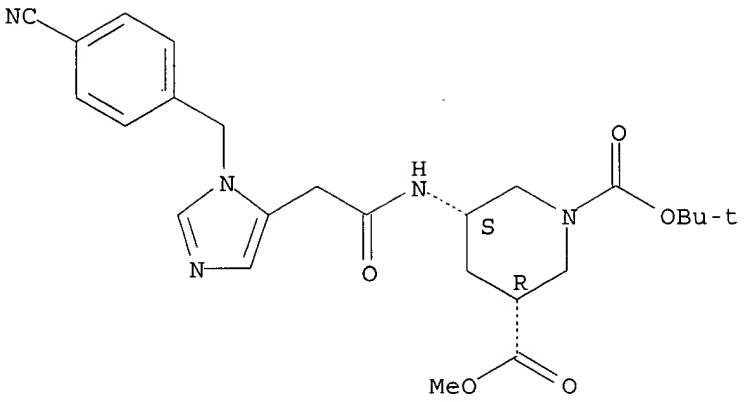
IT 59-51-8, Methionine 76-83-5, Chlorotriphenylmethane 83-01-2, Diphenylcarbamoyl chloride 98-59-9, Tosyl chloride 100-51-6, Benzyl alcohol, reactions 100-52-7, Benzaldehyde, reactions 100-69-6 103-71-9, Phenyl isocyanate, reactions 110-91-8, Morpholine, reactions 117-34-0, Diphenylacetic acid 122-78-1, Phenylacetaldehyde 498-95-3, Nipecotic acid 499-81-0, Pyridine-3,5-dicarboxylic acid 596-43-0, Triphenylmethyl bromide 603-33-8, Triphenylbismuth 776-74-9, Bromodiphenylmethane 947-91-1, Diphenylacetaldehyde 1016-78-0, 3-Chlorobenzophenone 1072-84-0, 1H-Imidazole-4-carboxylic acid 1074-59-5, 1H-Imidazole-4-propanoic acid 1939-99-7, .alpha.-Toluenesulfonyl chloride 2746-25-0, 4-Methoxybenzyl bromide 3251-69-2, 1H-Imidazole-4-acetic acid hydrochloride 3891-07-4 5006-62-2, Ethyl nipecotate 7114-36-5 17201-43-3, .alpha.-Bromo-p-tolunitrile 24424-99-5, Di-tert-butyl dicarbonate 26919-48-2 36713-38-9 51721-15-4 99161-89-4 191544-94-2 191544-95-3 191544-97-5 191544-98-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of imidazolyl-substituted piperidines as inhibitors of farnesyl-protein transferase)

IT 25761-05-1P 33769-07-2P 37675-18-6P 51718-80-0P 71827-53-7P 71827-54-8P 88495-54-9P 145133-11-5P 169503-35-9P 179026-34-7P 179026-35-8P 183500-34-7P 183500-35-8P 183500-36-9P 186202-42-6P 191544-70-4P 191544-71-5P 191544-72-6P 191544-73-7P 191544-75-9P 191544-76-0P 191544-77-1P **191544-78-2P** 191544-79-3P 191544-80-6P 191544-81-7P 191544-82-8P 191544-83-9P 191544-84-0P 191544-85-1P 191544-86-2P 191544-87-3P 191544-88-4P 191544-89-5P 191544-90-8P 191544-91-9P 191544-92-0P 191544-93-1P 191544-96-4P 191599-51-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of imidazolyl-substituted piperidines as inhibitors of farnesyl-protein transferase)

IT **191543-60-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of imidazolyl-substituted piperidines as inhibitors of farnesyl-protein transferase)

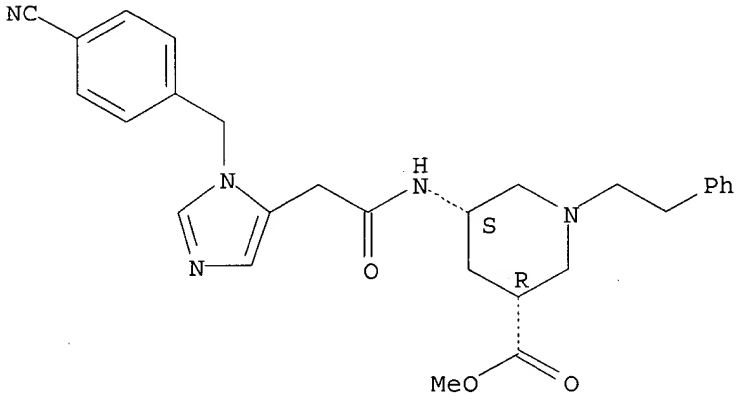
RN 191543-60-9 CAPLUS
CN 1,3-Piperidinedicarboxylic acid, 5-[[[1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]acetyl]amino]-, 1-(1,1-dimethylethyl) 3-methyl ester, (3R,5S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



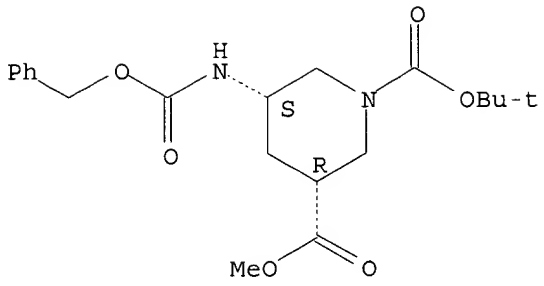
IT **191543-62-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of imidazolyl-substituted piperidines as inhibitors of farnesyl-protein transferase)
RN 191543-62-1 CAPLUS
CN 3-Piperidinecarboxylic acid, 5-[[[1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]acetyl]amino]-1-(2-phenylethyl)-, methyl ester, (3R,5S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



IT **191544-78-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of imidazolyl-substituted piperidines as inhibitors of farnesyl-protein transferase)
RN 191544-78-2 CAPLUS
CN 1,3-Piperidinedicarboxylic acid, 5-[[(phenylmethoxy)carbonyl]amino]-, 1-(1,1-dimethylethyl) 3-methyl ester, (3R,5S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.


Ph
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OBu-t
R
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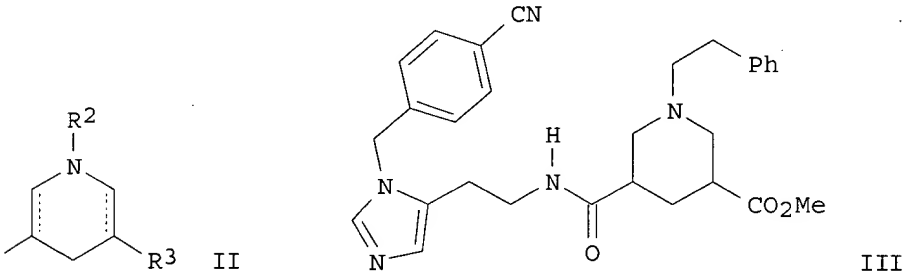
L10 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2003 ACS
AN 1998:650039 CAPLUS
DN 129:290134
TI Preparation of 3-[(imidazolylethyl)carbamoyl]piperidines as farnesyl-protein transferase inhibitors
IN Kim, Byeong M.; Shaw, Anthony W.; Graham, Samuel L.; Desolms, S. Jane; Ciccarone, Terrence M.
PA Merck and Co., Inc., USA
SO U.S., 55 pp.
CODEN: USXXAM
DT Patent
LA English
IC ICM A61K031-445
ICS C07D401-12
NCL 514326000
CC 28-9 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5817678	A	19981006	US 1996-749254	19961115
	US 6127366	A	20001003	US 1998-166271	19981005
PRAI	US 1995-7498P	P	19951122		
	US 1996-749254	A3	19961115		

OS MARPAT 129:290134
GI



AB (R4)rVA1[C(R1a)2]nA2[C(R1a)2]n[W(R5)s]t[C(R1b)2]pX[C(R1c)2]qR [I; R = piperidinyl group II; R1a,R1b,R1c = H, (ar)alkyl, alkoxy, aryl, etc.; R2 = H, alkyl, acyl, aryl, etc.; R3 = alkanoyl, aroyl, (un)substituted CONH2, alkylsulfonyl, etc.; R4 = H, halo, alkyl, alkoxy, etc.; A1,A2 = bond, CH:CH, O, CO, NH, etc.; V = H when r = 0, alkylene, arylene, etc.; W = heterocyclylene; X = bond, CONH, O, CO, etc.; dashed lines = optional bonds; n,p,q = 0-4; r = 0-5; s = 1 or 2; t = 0 or 1] were prepd. Thus, Me 1-tert-butoxycarbonyl-cis-5-carboxy-3-piperidinecarboxylate was amidated by 3-(4-cyanobenzyl)histamine (prepn. each given) and the deprotected product treated with PhCH2CHO/NaBH3CN to give title compd. cis-III. Data for biol. activity of I were given.
ST imidazolylethylcarbamoylpiperidine prepn farnesyl protein transferase inhibitor
IT Farnesylation
(oncogene protein Ras; prepn. of 3-[(imidazolylethyl)carbamoyl]piperidines as farnesyl-protein transferase inhibitors)
IT 131384-38-8
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(mediated disorders; treatment; prepn. of 3-[(imidazolylethyl)carbamoyl]piperidines as farnesyl-protein transferase

inhibitors)

IT 191543-37-0P 191543-38-1P 191543-39-2P 191543-40-5P 191543-41-6P
191543-42-7P 191543-43-8P 191543-44-9P 191543-45-0P 191543-46-1P
191543-47-2P 191543-48-3P 191543-49-4P 191543-50-7P 191543-51-8P
191543-52-9P 191543-53-0P 191543-54-1P 191543-55-2P 191543-56-3P
191543-57-4P 191543-58-5P 191543-59-6P **191543-60-9P**
191543-62-1P 191543-64-3P 191543-66-5P 191543-68-7P
191543-70-1P 191543-72-3P 191543-74-5P 191543-76-7P 191543-77-8P
191543-79-0P 191543-81-4P 191543-83-6P 191543-85-8P 191543-87-0P
191543-89-2P 191543-91-6P 191543-92-7P 191543-94-9P 191543-96-1P
191543-98-3P 191544-00-0P 191544-02-2P 191544-03-3P 191544-04-4P
191544-05-5P 191544-07-7P 191544-08-8P 191544-12-4P 191544-13-5P
191544-14-6P 191544-15-7P 191544-18-0P 191544-20-4P 191544-23-7P
191544-25-9P 191544-26-0P 191544-27-1P 191544-29-3P 191544-30-6P
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191544-58-8P 191544-59-9P 191544-60-2P 191544-61-3P 191544-62-4P
191544-63-5P 191544-64-6P 191544-65-7P 191544-66-8P 191544-67-9P
191544-69-1P 214136-70-6P 214136-72-8P 214136-77-3P 214136-78-4P
214136-80-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 3-[(imidazolylethyl)carbamoyl]piperidines as farnesyl-protein transferase inhibitors)

IT 76-83-5, Trityl chloride 83-01-2, Diphenylcarbamoyl chloride 100-51-6, Benzenemethanol, reactions 100-69-6, 2-Vinylpyridine 110-91-8, Morpholine, reactions 117-34-0, Diphenylacetic acid 122-78-1, Phenylacetaldehyde 498-95-3, Nipecotic acid 499-81-0, Pyridine-3,5-dicarboxylic acid 596-43-0, Trityl bromide 603-33-8, Triphenylbismuth 776-74-9, Diphenylmethyl bromide 947-91-1, Diphenylacetaldehyde 1016-78-0, 3-Chlorobenzophenone 1072-84-0, 1H-Imidazole-4-carboxylic acid 1074-59-5, 1H-Imidazole-4-propionic acid 1939-99-7, .alpha.-Toluenesulfonyl chloride 2746-25-0, 4-Methoxybenzyl bromide 3251-69-2, 1H-Imidazole-4-acetic acid hydrochloride 3891-07-4, N-(2-Hydroxyethyl)phthalimide 5006-62-2, Ethyl nipecotate 7114-36-5 10332-17-9, Methionine methyl ester 17201-43-3, 4-Cyanobenzyl bromide 26919-48-2, Bismuthine, tris(3-methylphenyl- 32673-41-9, 4-Hydroxymethylimidazole hydrochloride 34392-54-6, 2-Methylhistamine 36713-38-9 99161-89-4, 2-Phenyl-2-(2-pyridyl)oxirane
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of 3-[(imidazolylethyl)carbamoyl]piperidines as farnesyl-protein transferase inhibitors)

IT 33769-07-2P 37675-18-6P, (S)-Ethyl nipecotate 51718-80-0P
51721-15-4P 71827-53-7P 71827-54-8P 88495-54-9P 145133-11-5P
157226-85-2P 179026-34-7P 179026-35-8P 183500-34-7P 183500-35-8P
183500-36-9P 186202-42-6P 191544-70-4P 191544-72-6P 191544-73-7P
191544-75-9P 191544-76-0P 191544-77-1P **191544-78-2P**
191544-79-3P 191544-81-7P, 1-(2,2-Diphenylethyl)piperidine-3-carboxylic acid 191544-82-8P 191544-83-9P 191544-84-0P 191544-85-1P
191544-86-2P 191544-87-3P 191544-88-4P 191544-89-5P 191544-91-9P
191544-96-4P 191599-51-6P 214136-82-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of 3-[(imidazolylethyl)carbamoyl]piperidines as farnesyl-protein transferase inhibitors)

RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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(2) Anthony; US 5571835 1996 CAPLUS
(3) Breslin; US 5585359 1996 CAPLUS
(4) Brown; US 5141851 1992 CAPLUS
(5) Ciccarone; US 5534537 1996 CAPLUS

(6) de Solms; US 5326773 1994 CAPLUS
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(9) de Solms; US 5491164 1996 CAPLUS
(10) Deana; US 5352705 1994 CAPLUS
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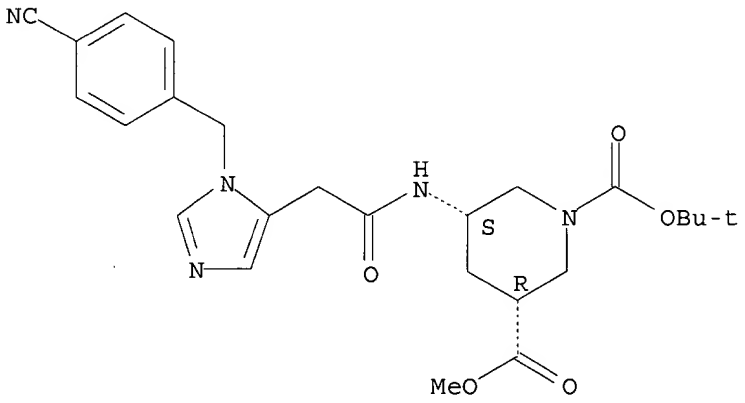
(27) Pompliano, D; Biochemistry 1992, V31, P3800 CAPLUS
(28) Sepp-Lorenzino, L; Cancer Research 1995, V55, P5302 CAPLUS
(29) Yuan; US 5478934 1995 CAPLUS

IT **191543-60-9P 191543-62-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 3-[(imidazolylethyl)carbamoyl]piperidines as farnesyl-protein transferase inhibitors)

RN 191543-60-9 CAPLUS

CN 1,3-Piperidinedicarboxylic acid, 5-[[[1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]acetyl]amino]-, 1-(1,1-dimethylethyl) 3-methyl ester, (3R,5S)-rel- (9CI) (CA INDEX NAME)

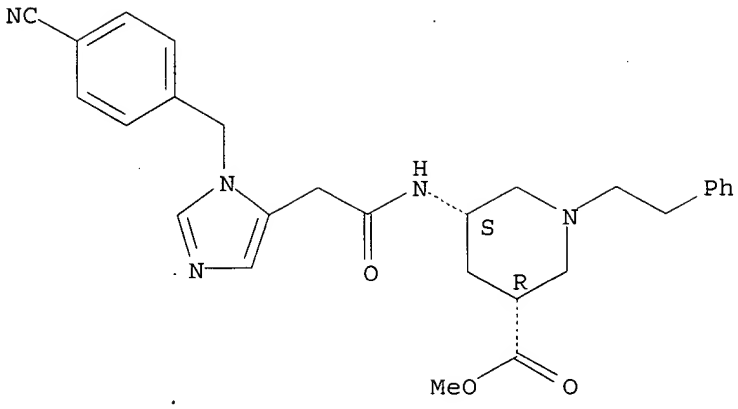
Relative stereochemistry.



RN 191543-62-1 CAPLUS

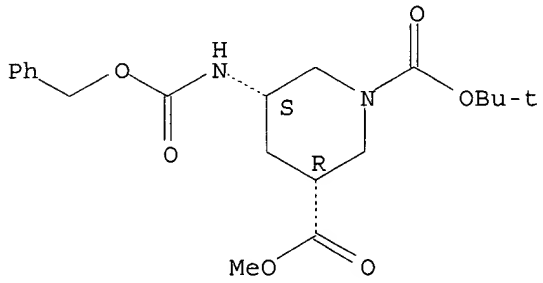
CN 3-Piperidinecarboxylic acid, 5-[[[1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]acetyl]amino]-1-(2-phenylethyl)-, methyl ester, (3R,5S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



IT **191544-78-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of 3-[(imidazolylethyl)carbamoyl]piperidines as farnesyl-protein transferase inhibitors)
RN 191544-78-2 CAPLUS
CN 1,3-Piperidinedicarboxylic acid, 5-[[(phenylmethoxy)carbonyl]amino]-, 1-(1,1-dimethylethyl) 3-methyl ester, (3R,5S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L11 ANSWER 3 OF 3 USPATFULL

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191544-63-5P 191544-64-6P 191544-65-7P 191544-66-8P 191544-67-9P
191544-69-1P 214136-70-6P 214136-72-8P 214136-77-3P 214136-78-4P
214136-80-8P
(prepn. of 3-[(imidazolylethyl)carbamoyl]piperidines as farnesyl-protein transferase inhibitors)

IT 33769-07-2P 37675-18-6P, (S)-Ethyl nipecotate 51718-80-0P
51721-15-4P 71827-53-7P 71827-54-8P 88495-54-9P 145133-11-5P
157226-85-2P 179026-34-7P 179026-35-8P 183500-34-7P 183500-35-8P
183500-36-9P 186202-42-6P 191544-70-4P 191544-72-6P 191544-73-7P
191544-75-9P 191544-76-0P 191544-77-1P **191544-78-2P**
191544-79-3P 191544-81-7P, 1-(2,2-Diphenylethyl)piperidine-3-carboxylic acid 191544-82-8P 191544-83-9P 191544-84-0P 191544-85-1P
191544-86-2P 191544-87-3P 191544-88-4P 191544-89-5P 191544-91-9P
191544-96-4P 191599-51-6P 214136-82-0P
(prepn. of 3-[(imidazolylethyl)carbamoyl]piperidines as farnesyl-protein transferase inhibitors)

ACCESSION NUMBER: 1998:122428 USPATFULL
TITLE: Inhibitors of farnesyl-protein transferase
INVENTOR(S): Kim, Byeong M., Seoul, Korea, Republic of
Shaw, Anthony W., Lansdale, PA, United States
Graham, Samuel L., Schwenksville, PA, United States
deSolms, S. Jane, Norristown, PA, United States
Ciccarone, Terrence M., Telford, PA, United States
PATENT ASSIGNEE(S): Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5817678		19981006	
APPLICATION INFO.:	US 1996-749254		19961115	(8)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1995-7498P	19951122 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Fan, Jane
LEGAL REPRESENTATIVE: Muthard, David A., Daniel, Mark R.
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
LINE COUNT: 3498
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

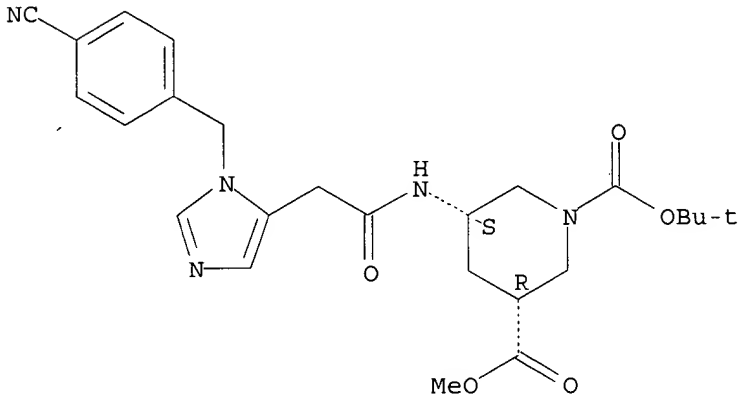
IT **191543-60-9P 191543-62-1P**
(prepn. of 3-[(imidazolylethyl)carbamoyl]piperidines as

farnesyl-protein transferase inhibitors)

RN 191543-60-9 USPATFULL

CN 1,3-Piperidinedicarboxylic acid, 5-[[[1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]acetyl]amino]-, 1-(1,1-dimethylethyl) 3-methyl ester, (3R,5S)-rel- (9CI) (CA INDEX NAME)

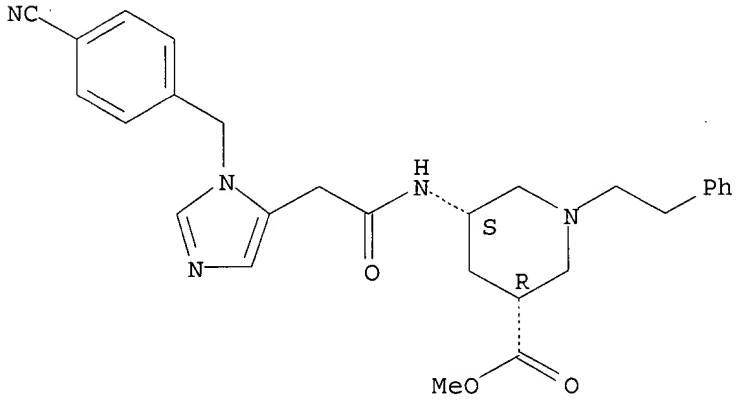
Relative stereochemistry.



RN 191543-62-1 USPATFULL

CN 3-Piperidinecarboxylic acid, 5-[[[1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]acetyl]amino]-1-(2-phenylethyl)-, methyl ester, (3R,5S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



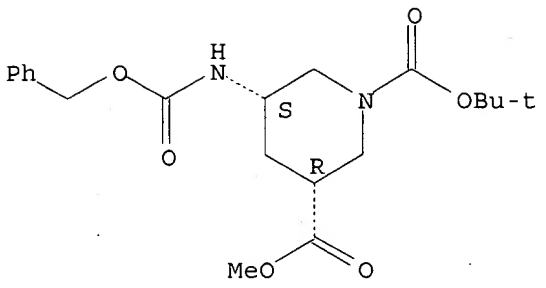
IT **191544-78-2P**

(prepn. of 3-[(imidazolylethyl)carbamoyl]piperidines as farnesyl-protein transferase inhibitors)

RN 191544-78-2 USPATFULL

CN 1,3-Piperidinedicarboxylic acid, 5-[[(phenylmethoxy)carbonyl]amino]-, 1-(1,1-dimethylethyl) 3-methyl ester, (3R,5S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.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L11 ANSWER 1 OF 3 USPATFULL

IT 191543-37-0P 191543-38-1P 191543-39-2P 191543-57-4P
191543-60-9P 191543-79-0P
(prepn. of imidazolyl-substituted piperidines as inhibitors of farnesyl-protein transferase)

IT 191543-40-5P 191543-41-6P 191543-42-7P 191543-43-8P 191543-44-9P
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191544-60-2P 191544-61-3P 191544-62-4P 191544-63-5P 191544-64-6P
191544-65-7P 191544-66-8P 191544-67-9P 191544-68-0P 191544-69-1P
(prepn. of imidazolyl-substituted piperidines as inhibitors of farnesyl-protein transferase)

IT 25761-05-1P 33769-07-2P 37675-18-6P 51718-80-0P 71827-53-7P
71827-54-8P 88495-54-9P 145133-11-5P 169503-35-9P 179026-34-7P
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191599-51-6P
(prepn. of imidazolyl-substituted piperidines as inhibitors of farnesyl-protein transferase)

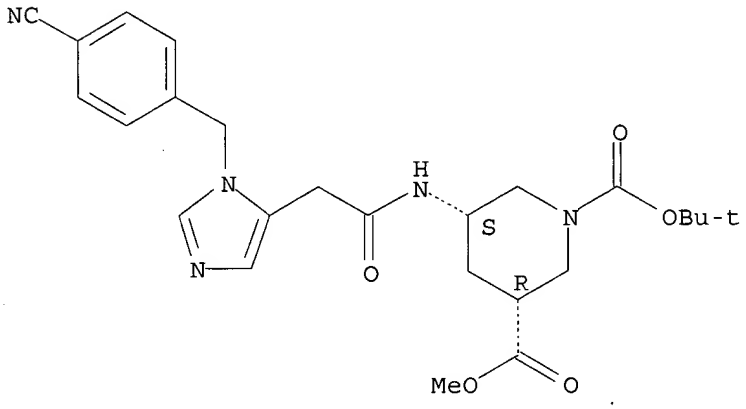
ACCESSION NUMBER: 2000:131838 USPATFULL
TITLE: Inhibitors of farnesyl-protein transferase
INVENTOR(S): Kim, Byeong M., Seoul, Korea, Republic of
Shaw, Anthony W., Lansdale, PA, United States
Graham, Samuel L., Schwenksville, PA, United States
deSolms, S. Jane, Norristown, PA, United States
Ciccarone, Terrence M., Telford, PA, United States
PATENT ASSIGNEE(S): Merck & Co., Inc., Rahway, NJ, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6127366		20001003
APPLICATION INFO.:	US 1998-166271		19981005 (9)

RELATED APPLN. INFO.: Division of Ser. No. US 1996-749254, filed on 15 Nov 1996, now patented, Pat. No. US 5817678
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Fan, Jane
LEGAL REPRESENTATIVE: Garcia-Rivas, J. Antonio, Daniel, Mark R.
NUMBER OF CLAIMS: 22
EXEMPLARY CLAIM: 1
LINE COUNT: 3441
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

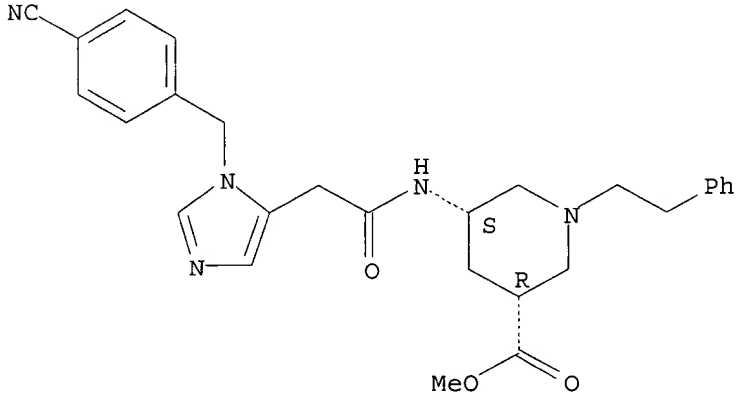
IT **191543-60-9P**
(prepn. of imidazolyl-substituted piperidines as inhibitors of farnesyl-protein transferase)
RN 191543-60-9 USPATFULL
CN 1,3-Piperidinedicarboxylic acid, 5-[[[1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]acetyl]amino]-, 1-(1,1-dimethylethyl) 3-methyl ester, (3R,5S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



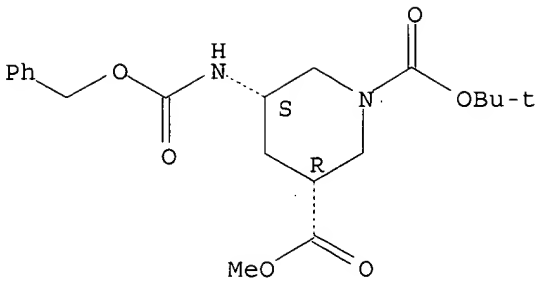
IT **191543-62-1P**
(prepn. of imidazolyl-substituted piperidines as inhibitors of farnesyl-protein transferase)
RN 191543-62-1 USPATFULL
CN 3-Piperidinecarboxylic acid, 5-[[[1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]acetyl]amino]-1-(2-phenylethyl)-, methyl ester, (3R,5S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



IT **191544-78-2P**
(prepn. of imidazolyl-substituted piperidines as inhibitors of farnesyl-protein transferase)
RN 191544-78-2 USPATFULL
CN 1,3-Piperidinedicarboxylic acid, 5-[[(phenylmethoxy)carbonyl]amino]-, 1-(1,1-dimethylethyl) 3-methyl ester, (3R,5S)-rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.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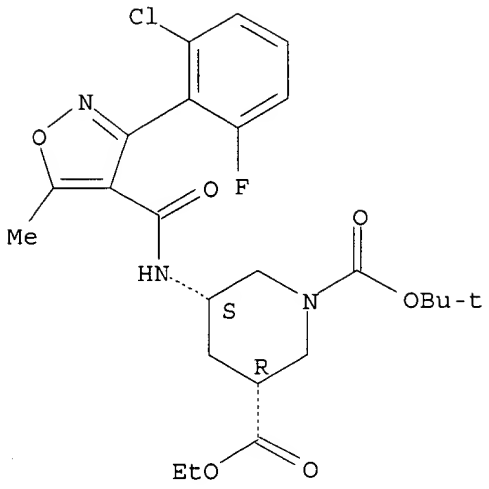

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 2 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 471895-13-3 REGISTRY
CN 1,3-Piperidinedicarboxylic acid, 5-[[[2-(trimethylsilyl)ethoxy]carbonyl]amino]-, 1-(1,1-dimethylethyl) 3-ethyl ester (9CI) (CA INDEX NAME)
FS 3D CONCORD
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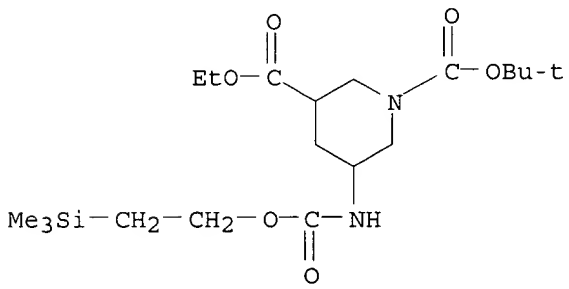
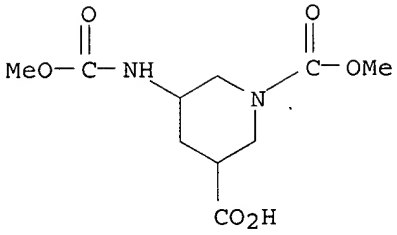
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 3 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 345219-87-6 REGISTRY
CN 1,3-Piperidinedicarboxylic acid, 5-[(methoxycarbonyl)amino]-, 1-methyl ester (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C10 H16 N2 O6
SR Reaction Database
LC STN Files: CASREACT



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L2 ANSWER 4 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 315700-20-0 REGISTRY
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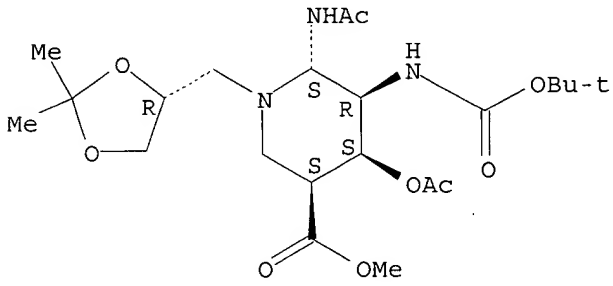
FS STEREOSEARCH
MF C22 H37 N3 O9
SR CA
LC STN Files: CA, CAPLUS, CASREACT

Absolute stereochemistry.

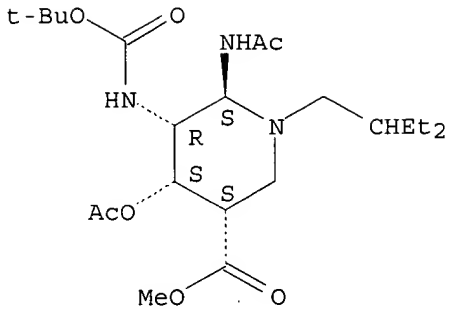


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 5 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 315700-18-6 REGISTRY
CN 3-Piperidinecarboxylic acid, 6-(acetylamino)-4-(acetyloxy)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-1-(2-ethylbutyl)-, methyl ester, (3S,4S,5R,6S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C22 H39 N3 O7
SR CA
LC STN Files: CA, CAPLUS, CASREACT

Absolute stereochemistry. Rotation (-).

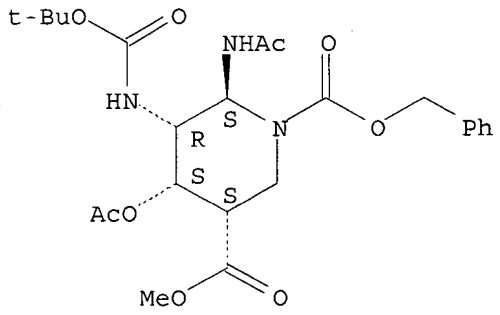


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 6 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 315700-16-4 REGISTRY
CN 1,3-Piperidinedicarboxylic acid, 6-(acetylamino)-4-(acetyloxy)-5-[[(1,1-dimethylethoxy)carbonyl]amino]-, 3-methyl 1-(phenylmethyl) ester, (3S,4S,5R,6S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C24 H33 N3 O9
SR CA
LC STN Files: CA, CAPLUS, CASREACT

Absolute stereochemistry. Rotation (+).

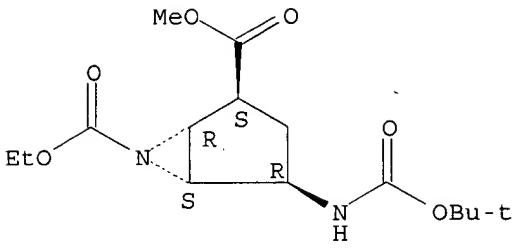


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 7 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 294673-95-3 REGISTRY
CN 6-Azabicyclo[3.1.0]hexane-2,6-dicarboxylic acid, 4-[[(1,1-dimethylethoxy)carbonyl]amino]-, 6-ethyl 2-methyl ester, (1R,2S,4R,5S)-rel- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C15 H24 N2 O6
SR CA
LC STN Files: CA, CAPLUS, CASREACT

Relative stereochemistry.

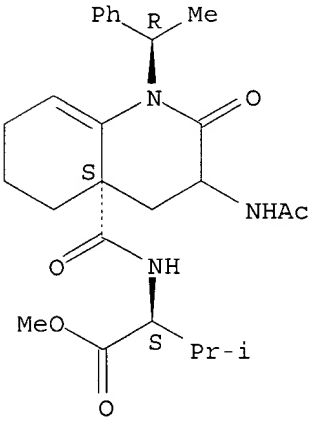


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 8 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 203314-79-8 REGISTRY
CN L-Valine, N-[[(4aS)-3-(acetylamino)-1,3,4,5,6,7-hexahydro-2-oxo-1-[(1R)-1-phenylethyl]-4a(2H)-quinolinyl]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C26 H35 N3 O5
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

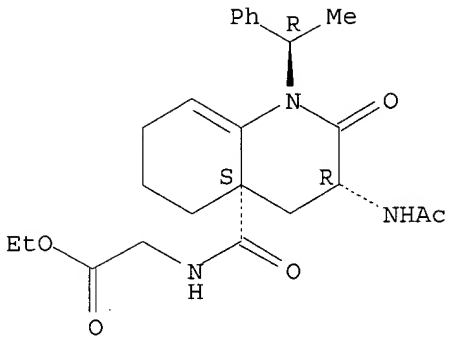


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 9 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 203314-78-7 REGISTRY
CN Glycine, N-[[(3R,4aS)-3-(acetylamino)-1,3,4,5,6,7-hexahydro-2-oxo-1-[(1R)-1-phenylethyl]-4a(2H)-quinolinyl]carbonyl]-, ethyl ester (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C24 H31 N3 O5
SR CA
LC STN Files: CA, CAPLUS, CASREACT

Absolute stereochemistry.

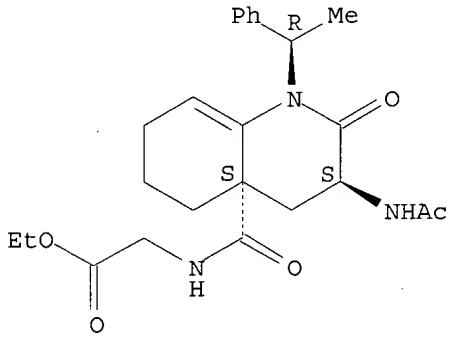


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 10 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 203314-77-6 REGISTRY
CN Glycine, N-[[(3S,4aS)-3-(acetylamino)-1,3,4,5,6,7-hexahydro-2-oxo-1-[(1R)-1-phenylethyl]-4a(2H)-quinolinyl]carbonyl]-, ethyl ester (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C24 H31 N3 O5
SR CA
LC STN Files: CA, CAPLUS, CASREACT

Absolute stereochemistry.

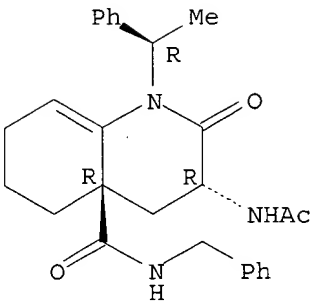


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 11 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 203314-75-4 REGISTRY
CN 4a(2H)-Quinolinecarboxamide, 3-(acetylamino)-1,3,4,5,6,7-hexahydro-2-oxo-1-(1-phenylethyl)-N-(phenylmethyl)-, [3R-[1(R*),3.alpha.,4a.beta.]]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C27 H31 N3 O3
SR CA
LC STN Files: CA, CAPLUS, CASREACT

Absolute stereochemistry.

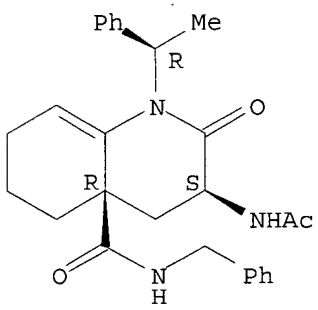


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 12 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 203314-74-3 REGISTRY
CN 4a(2H)-Quinolinecarboxamide, 3-(acetylamino)-1,3,4,5,6,7-hexahydro-2-oxo-1-(1-phenylethyl)-N-(phenylmethyl)-, [3S-[1(S*),3.alpha.,4a.alpha.]]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C27 H31 N3 O3
SR CA
LC STN Files: CA, CAPLUS, CASREACT

Absolute stereochemistry. Rotation (-).

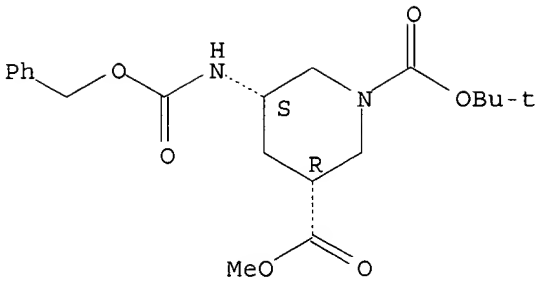


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 13 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 191544-78-2 REGISTRY
CN 1,3-Piperidinedicarboxylic acid, 5-[[(phenylmethoxy)carbonyl]amino]-, 1-(1,1-dimethylethyl) 3-methyl ester, (3R,5S)-rel- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,3-Piperidinedicarboxylic acid, 5-[[(phenylmethoxy)carbonyl]amino]-, 1-(1,1-dimethylethyl) 3-methyl ester, cis-
FS STEREOSEARCH
MF C20 H28 N2 O6
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Relative stereochemistry.

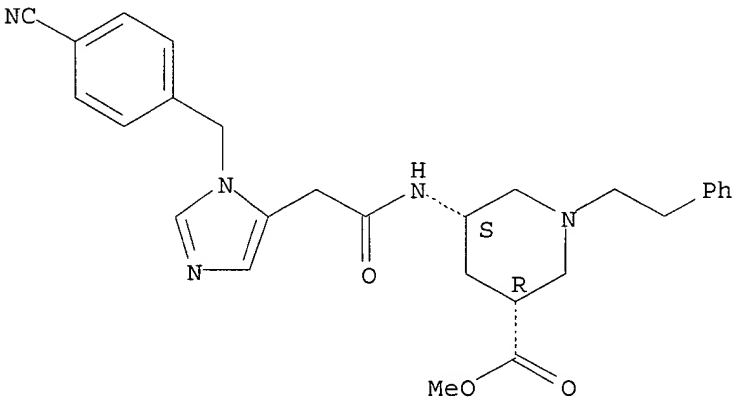


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1957 TO DATE)
2 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 14 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 191543-62-1 REGISTRY
CN 3-Piperidinecarboxylic acid, 5-[[[1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]acetyl]amino]-1-(2-phenylethyl)-, methyl ester, (3R,5S)-rel- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3-Piperidinecarboxylic acid, 5-[[[1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]acetyl]amino]-1-(2-phenylethyl)-, methyl ester, cis-
FS STEREOSEARCH
MF C28 H31 N5 O3
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Relative stereochemistry.



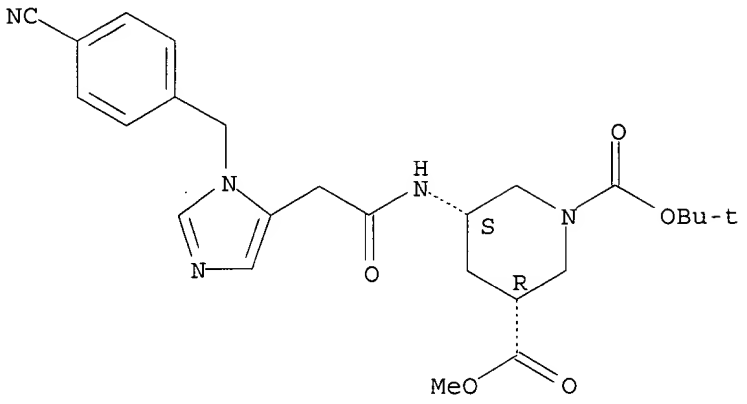
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1957 TO DATE)
2 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 15 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 191543-60-9 REGISTRY
CN 1,3-Piperidinedicarboxylic acid, 5-[[[1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]acetyl]amino]-, 1-(1,1-dimethylethyl) 3-methyl ester, (3R,5S)-rel- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,3-Piperidinedicarboxylic acid, 5-[[[1-[(4-cyanophenyl)methyl]-1H-imidazol-5-yl]acetyl]amino]-, 1-(1,1-dimethylethyl) 3-methyl ester, cis-
FS STEREOSEARCH

MF C25 H31 N5 O5
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Relative stereochemistry.

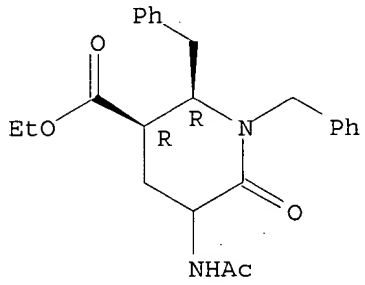


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1957 TO DATE)
2 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 16 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 185856-26-2 REGISTRY
CN 3-Piperidinecarboxylic acid, 5-(acetylamino)-6-oxo-1,2-bis(phenylmethyl)-, ethyl ester, (2R,3R)-[partial]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C24 H28 N2 O4
SR CA
LC STN Files: CA, CAPLUS

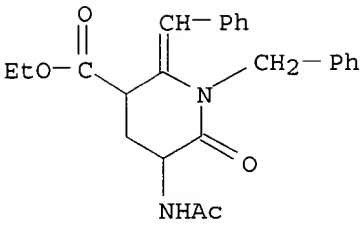
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 17 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 185856-25-1 REGISTRY
CN 3-Piperidinecarboxylic acid, 5-(acetylamino)-6-oxo-1-(phenylmethyl)-2-(phenylmethylene)-, ethyl ester (9CI) (CA INDEX NAME)
MF C24 H26 N2 O4
SR CA
LC STN Files: CA, CAPLUS

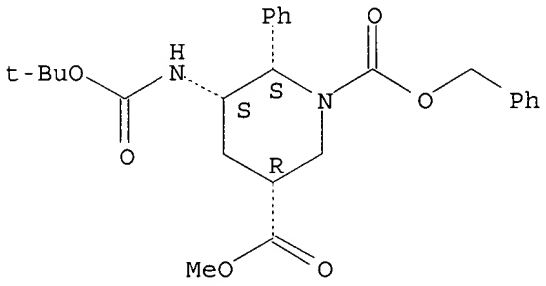


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 18 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 168321-57-1 REGISTRY
CN 1,3-Piperidinedicarboxylic acid, 5-[[(1,1-dimethylethoxy)carbonyl]amino]-6-phenyl-, 3-methyl 1-(phenylmethyl) ester, (3.alpha.,5.alpha.,6.alpha.)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C26 H32 N2 O6
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Relative stereochemistry.

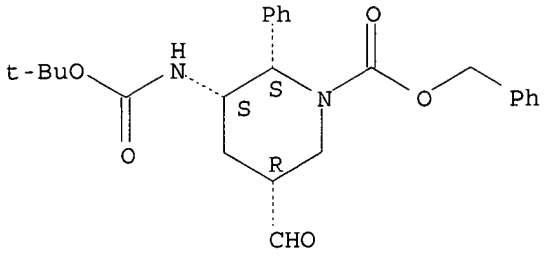


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 19 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 168321-56-0 REGISTRY
CN 1-Piperidinecarboxylic acid, 3-[[(1,1-dimethylethoxy)carbonyl]amino]-5-formyl-2-phenyl-, phenylmethyl ester, (2.alpha.,3.alpha.,5.alpha.)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C25 H30 N2 O5
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Relative stereochemistry.

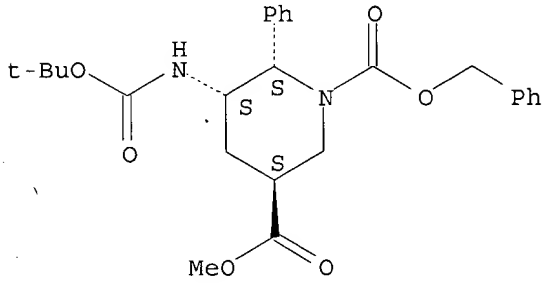


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 20 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 168321-42-4 REGISTRY
CN 1,3-Piperidinedicarboxylic acid, 5-[[(1,1-dimethylethoxy)carbonyl]amino]-6-phenyl-, 3-methyl 1-(phenylmethyl) ester, (3.alpha.,5.beta.,6.beta.)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C26 H32 N2 O6
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Relative stereochemistry.

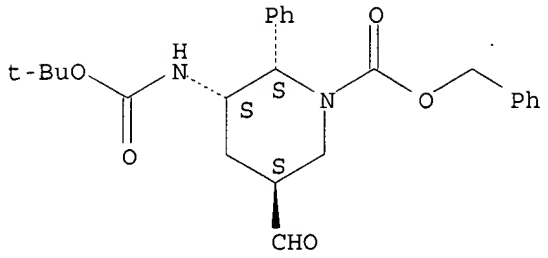


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 21 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 168321-41-3 REGISTRY
CN 1-Piperidinecarboxylic acid, 3-[[(1,1-dimethylethoxy)carbonyl]amino]-5-formyl-2-phenyl-, phenylmethyl ester, (2.alpha.,3.alpha.,5.beta.)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C25 H30 N2 O5
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Relative stereochemistry.

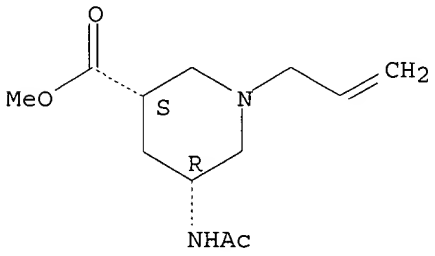


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 22 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 162314-93-4 REGISTRY
CN 3-Piperidinecarboxylic acid, 5-(acetylamino)-1-(2-propenyl)-, methyl ester, cis- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3-Piperidinecarboxylic acid, 5-(acetylamino)-1-(2-propenyl)-, methyl ester, cis-(.+-.)-
FS STEREOSEARCH
MF C12 H20 N2 O3
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Relative stereochemistry.

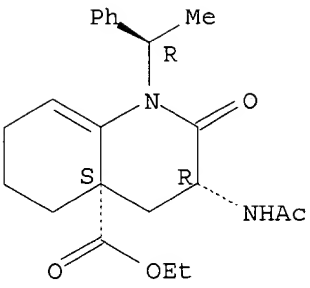


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 23 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 156148-81-1 REGISTRY
CN 4a(2H)-Quinolinecarboxylic acid, 3-(acetylamino)-1,3,4,5,6,7-hexahydro-2-oxo-1-(1-phenylethyl)-, ethyl ester, [3R-[1(R*),3.alpha.,4a.alpha.]]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C22 H28 N2 O4
SR CA
LC STN Files: CA, CAPLUS, CASREACT

Absolute stereochemistry.

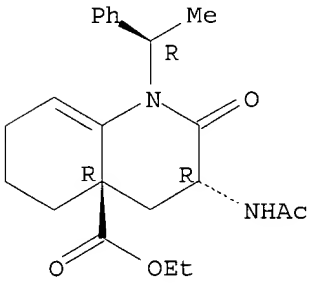


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 24 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 156148-79-7 REGISTRY
CN 4a(2H)-Quinolinecarboxylic acid, 3-(acetylamino)-1,3,4,5,6,7-hexahydro-2-oxo-1-(1-phenylethyl)-, ethyl ester, [3R-[1(R*),3.alpha.,4a.beta.]]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C22 H28 N2 O4
SR CA
LC STN Files: CA, CAPLUS, CASREACT

Absolute stereochemistry.

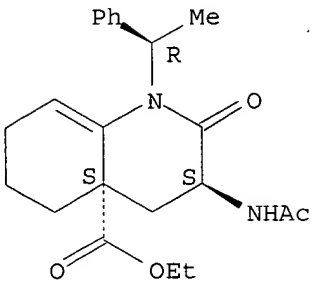


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 25 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 156148-75-3 REGISTRY
CN 4a(2H)-Quinolinecarboxylic acid, 3-(acetylamino)-1,3,4,5,6,7-hexahydro-2-oxo-1-(1-phenylethyl)-, ethyl ester, [3S-[1(S*),3.alpha.,4a.beta.]]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C22 H28 N2 O4
SR CA
LC STN Files: CA, CAPLUS, CASREACT

Absolute stereochemistry.

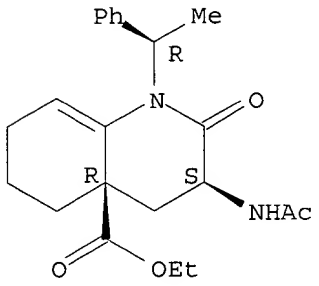


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 26 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 156148-71-9 REGISTRY
CN 4a(2H)-Quinolinecarboxylic acid, 3-(acetylamino)-1,3,4,5,6,7-hexahydro-2-oxo-1-(1-phenylethyl)-, ethyl ester, [3S-[1(S*),3.alpha.,4a.alpha.]]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C22 H28 N2 O4
SR CA
LC STN Files: CA, CAPLUS, CASREACT

Absolute stereochemistry.

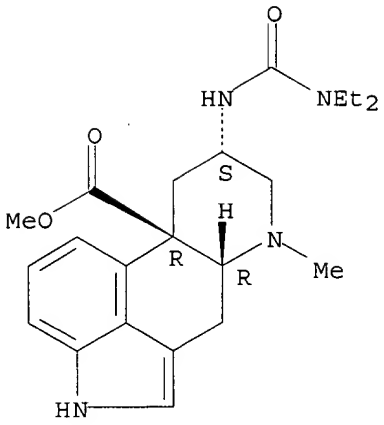


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 27 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 122923-22-2 REGISTRY
CN Ergoline-10-carboxylic acid, 8-[[(diethylamino)carbonyl]amino]-6-methyl-, methyl ester, (8.alpha.,10.beta.)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Indolo[4,3-fg]quinoline, ergoline-10-carboxylic acid deriv.
FS STEREOSEARCH
MF C22 H30 N4 O3
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT
(*File contains numerically searchable property data)

Absolute stereochemistry.

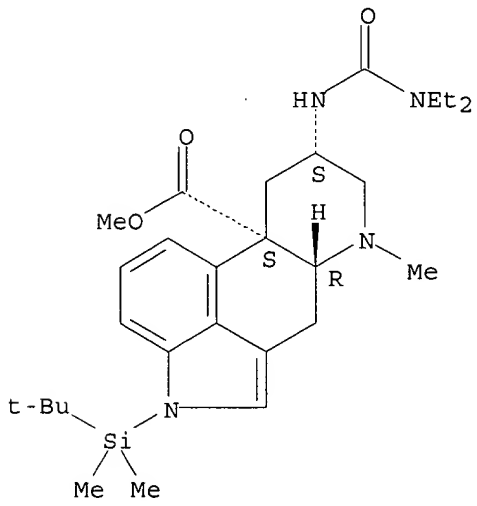


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 28 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 122923-20-0 REGISTRY
CN Ergoline-10-carboxylic acid, 8-[[(diethylamino)carbonyl]amino]-1-[(1,1-dimethylethyl)dimethylsilyl]-6-methyl-, methyl ester, (8.alpha.)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Indolo[4,3-fg]quinoline, ergoline-10-carboxylic acid deriv.
FS STEREOSEARCH
MF C28 H44 N4 O3 Si
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT
(*File contains numerically searchable property data)

Absolute stereochemistry.



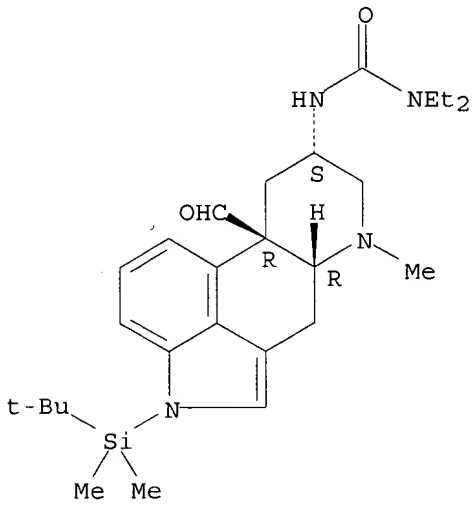
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)

1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 29 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 122923-19-7 REGISTRY
CN Urea, N'-[(8.alpha.,10.beta.)-1-[(1,1-dimethylethyl)dimethylsilyl]-10-formyl-6-methylergolin-8-yl]-N,N-diethyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Ergoline, urea deriv.
CN Indolo[4,3-fg]quinoline, urea deriv.
FS STEREOSEARCH
MF C27 H42 N4 O2 Si
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT
(*File contains numerically searchable property data)

Absolute stereochemistry.

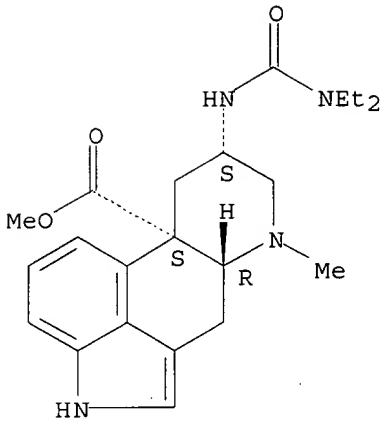


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 30 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 122888-37-3 REGISTRY
CN Ergoline-10-carboxylic acid, 8-[[(diethylamino)carbonyl]amino]-6-methyl-, methyl ester, (8.alpha.)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Indolo[4,3-fg]quinoline, ergoline-10-carboxylic acid deriv.
FS STEREOSEARCH
MF C22 H30 N4 O3
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT
(*File contains numerically searchable property data)

Absolute stereochemistry.

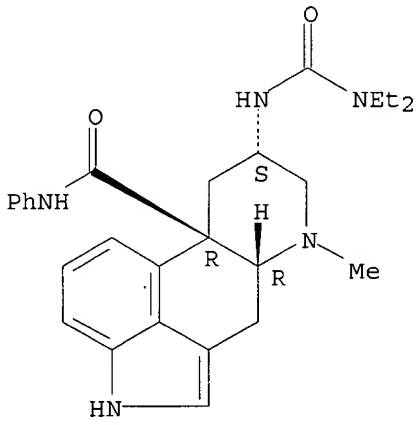


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 31 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 122888-36-2 REGISTRY
CN Ergoline-10-carboxamide, 8-[[(diethylamino)carbonyl]amino]-6-methyl-N-phenyl-, (8.alpha.,10.beta.)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Indolo[4,3-fg]quinoline, ergoline-10-carboxamide deriv.
FS STEREOSEARCH
MF C27 H33 N5 O2
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT
(*File contains numerically searchable property data)

Absolute stereochemistry.



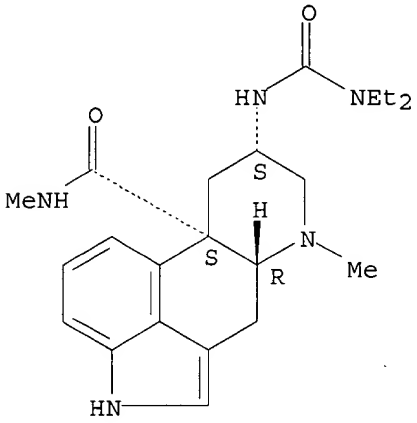
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 32 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 122888-35-1 REGISTRY
CN Ergoline-10-carboxamide, 8-[[(diethylamino)carbonyl]amino]-N,6-dimethyl-, (8.alpha.)- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:
CN Indolo[4,3-fg]quinoline, ergoline-10-carboxamide deriv.
FS STEREOSEARCH
MF C22 H31 N5 O2
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT
(*File contains numerically searchable property data)

Absolute stereochemistry.

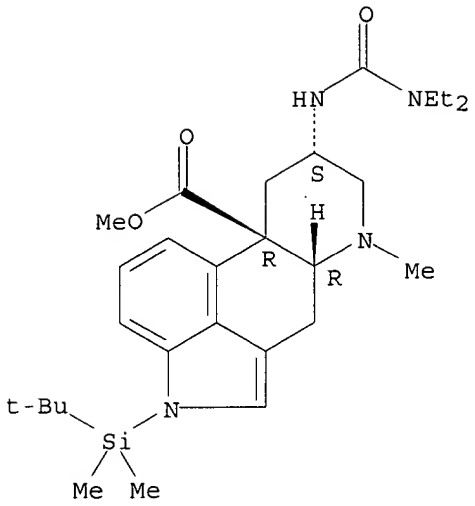


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 33 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 122888-34-0 REGISTRY
CN Ergoline-10-carboxylic acid, 8-[[(diethylamino)carbonyl]amino]-1-[(1,1-dimethylethyl)dimethylsilyl]-6-methyl-, methyl ester, (8.alpha.,10.beta.)-(9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Indolo[4,3-fg]quinoline, ergoline-10-carboxylic acid deriv.
FS STEREOSEARCH
MF C28 H44 N4 O3 Si
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT
(*File contains numerically searchable property data)

Absolute stereochemistry.

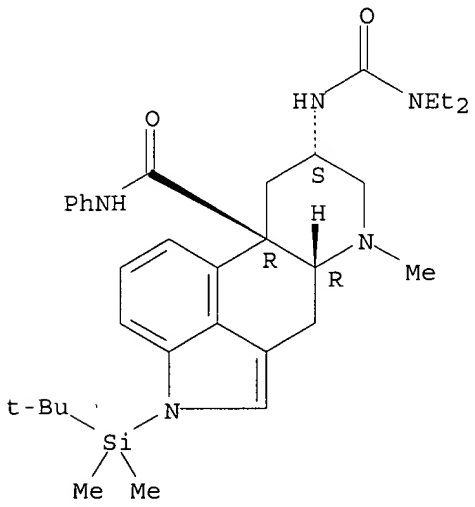


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 34 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 122888-33-9 REGISTRY
CN Ergoline-10-carboxamide, 8-[[(diethylamino)carbonyl]amino]-1-[(1,1-dimethylethyl)dimethylsilyl]-6-methyl-N-phenyl-, (8.alpha.,10.beta.)-(9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Indolo[4,3-fg]quinoline, ergoline-10-carboxamide deriv.
FS STEREOSEARCH
MF C33 H47 N5 O2 Si
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT
(*File contains numerically searchable property data)

Absolute stereochemistry.

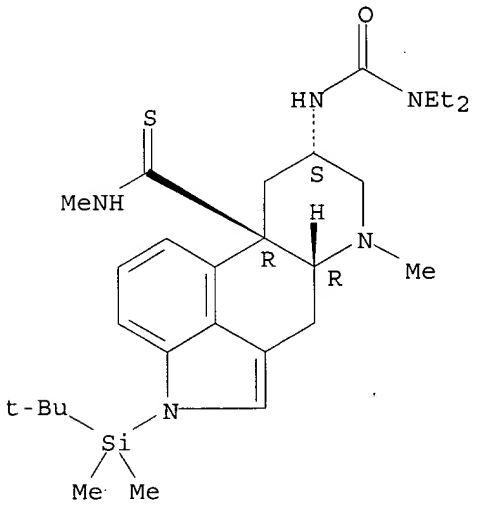


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 35 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 122888-32-8 REGISTRY
CN Ergoline-10-carbothioamide, 8-[[(diethylamino)carbonyl]amino]-1-[(1,1-dimethylethyl)dimethylsilyl]-N,6-dimethyl-, (8.alpha.,10.beta.)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Indolo[4,3-fg]quinoline, ergoline-10-carbothioamide deriv.
FS STEREOSEARCH
MF C28 H45 N5 O S Si
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT
(*File contains numerically searchable property data)

Absolute stereochemistry.

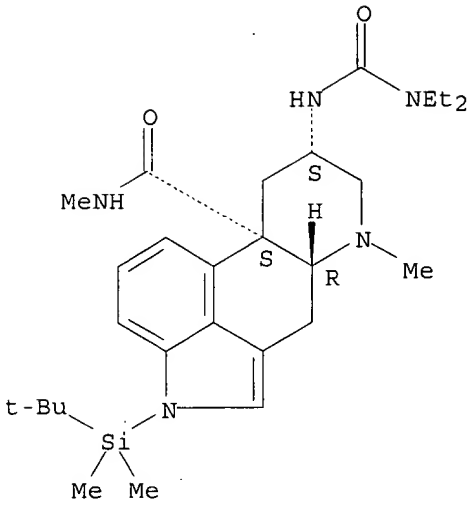


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 36 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 122888-31-7 REGISTRY
CN Ergoline-10-carboxamide, 8-[[(diethylamino)carbonyl]amino]-1-[(1,1-dimethylethyl)dimethylsilyl]-N,6-dimethyl-, (8.alpha.)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Indolo[4,3-fg]quinoline, ergoline-10-carboxamide deriv.
FS STEREOSEARCH
MF C28 H45 N5 O2 Si
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT
(*File contains numerically searchable property data)

Absolute stereochemistry.

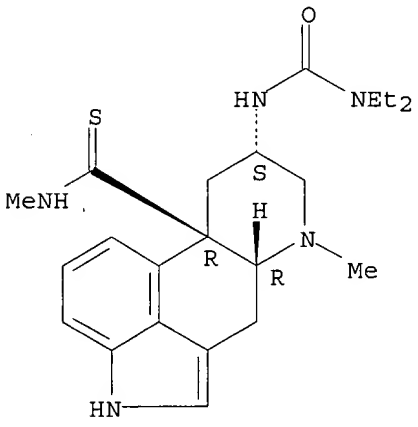


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 37 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 115092-03-0 REGISTRY
CN Ergoline-10-carbothioamide, 8-[[(diethylamino)carbonyl]amino]-N,6-dimethyl-, (8.alpha.,10.beta.)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Indolo[4,3-fg]quinoline, ergoline-10-carbothioamide deriv.
FS STEREOSEARCH
MF C22 H31 N5 O S
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT
(*File contains numerically searchable property data)

Absolute stereochemistry.

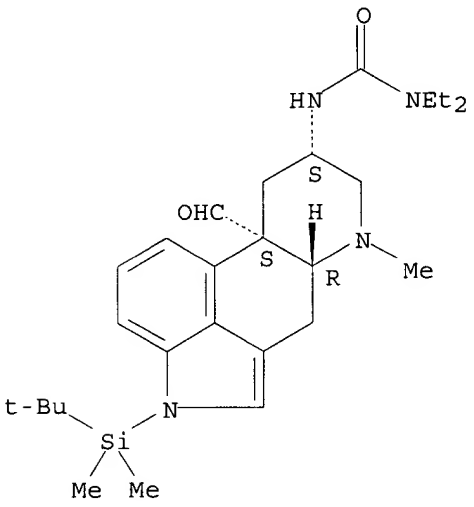


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1957 TO DATE)
2 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 38 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 115087-44-0 REGISTRY
CN Urea, N'-[(8.alpha.)-1-[(1,1-dimethylethyl)dimethylsilyl]-10-formyl-6-methylergolin-8-yl]-N,N-diethyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Ergoline, urea deriv.
CN Indolo[4,3-fg]quinoline, urea deriv.
FS STEREOSEARCH
MF C27 H42 N4 O2 Si
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT
(*File contains numerically searchable property data)

Absolute stereochemistry.

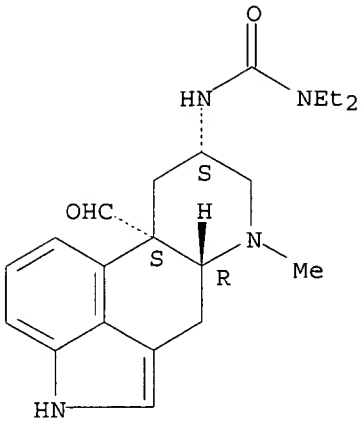


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1957 TO DATE)
2 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 39 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 115087-33-7 REGISTRY
CN Urea, N,N-diethyl-N'-[(8.alpha.)-10-formyl-6-methylergolin-8-yl]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Ergoline, urea deriv.
CN Indolo[4,3-fg]quinoline, urea deriv.
FS STEREOSEARCH
MF C21 H28 N4 O2
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT
(*File contains numerically searchable property data)

Absolute stereochemistry.

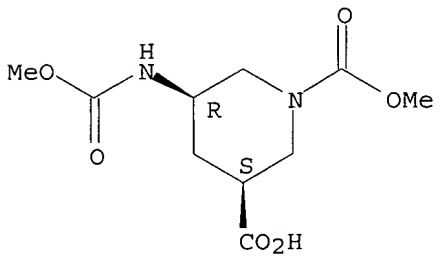


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

2 REFERENCES IN FILE CA (1957 TO DATE)
2 REFERENCES IN FILE CAPLUS (1957 TO DATE)

L2 ANSWER 40 OF 40 REGISTRY COPYRIGHT 2003 ACS
RN 80613-07-6 REGISTRY
CN 1,3-Piperidinedicarboxylic acid, 5-[(methoxycarbonyl)amino]-, 1-methyl ester, cis- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,3-Piperidinedicarboxylic acid, 5-[(methoxycarbonyl)amino]-, 1-methyl ester, cis-(.+-.)-
FS STEREOSEARCH
MF C10 H16 N2 O6
LC STN Files: CA, CAPLUS

Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1957 TO DATE)
1 REFERENCES IN FILE CAPLUS (1957 TO DATE)

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FILE 'HCAPLUS' ENTERED AT 13:35:56 ON 18 APR 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)
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FILE COVERS 1907 - 18 Apr 2003  VOL 138 ISS 17
FILE LAST UPDATED: 17 Apr 2003  (20030417/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


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L5              STR
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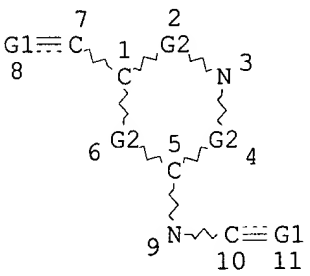


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REP G2=(0-2) C
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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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STEREO ATTRIBUTES: NONE
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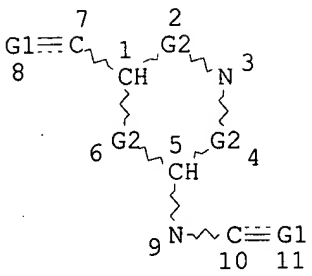

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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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NUMBER OF NODES IS 11

STEREO ATTRIBUTES: NONE
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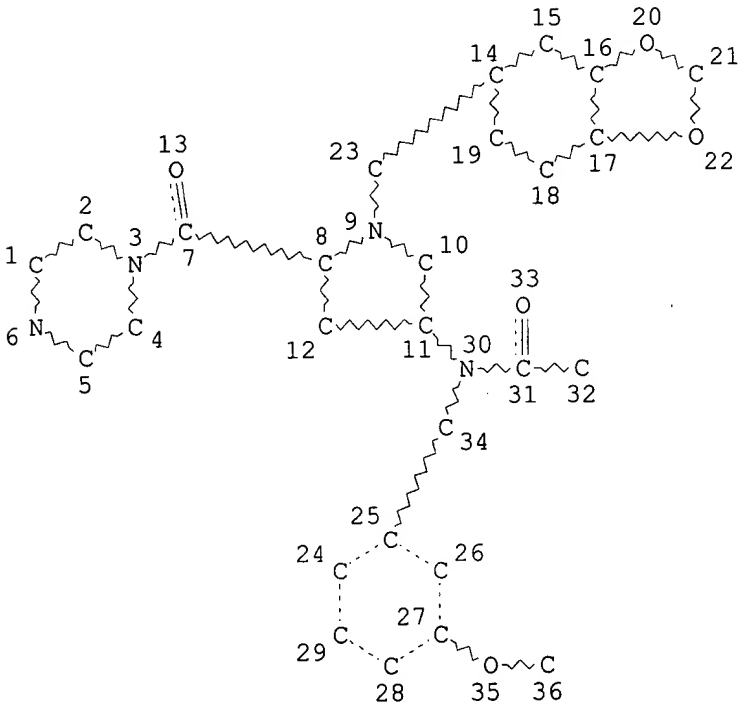
L10 STR



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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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NUMBER OF NODES IS 36

STEREO ATTRIBUTES: NONE
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L12 3 SEA FILE=HCAPLUS ABB=ON PLU=ON L11

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=> d ibib abs hitstr l12 1-3

L12 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:293477 HCAPLUS
DOCUMENT NUMBER: 136:304056
TITLE: Hedgehog antagonists, methods and uses related thereto
INVENTOR(S): Dudek, Henryk; Pepicelli, Carmen; Karavanov, Irina
PATENT ASSIGNEE(S): Curis, Inc., USA
SOURCE: PCT Int. Appl., 224 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002030462	A2	20020418	WO 2001-US32100	20011015
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002165221	A1	20021107	US 2001-977096	20011012
AU 2001096844	A5	20020422	AU 2001-96844	20011015

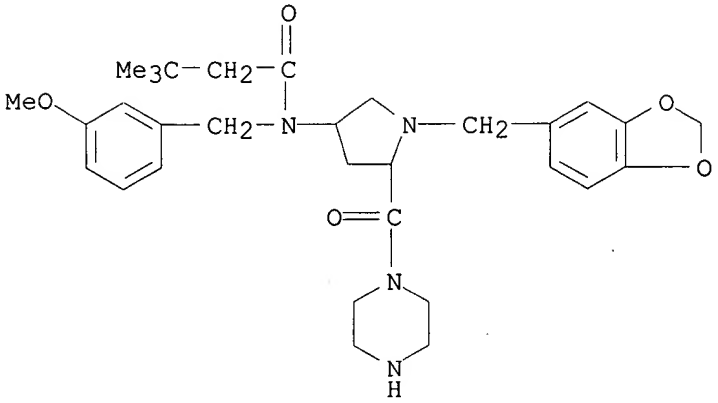
PRIORITY APPLN. INFO.: US 2000-240564P P 20001013
US 2000-240536P P 20001013
WO 2001-US32100 W 20011015

AB The present application is directed to compns. and methods for inhibiting angiogenesis and treating or preventing unwanted cell proliferation, including tumors, by inhibiting the hedgehog pathway, e.g., with an antagonist of the hedgehog pathway such as those disclosed herein. In one embodiment, the subject methods may be used to inhibit unwanted cell proliferation by detg. whether cells overexpress a gli gene, and contacting cells that overexpress gli gene with an effective amt. of a hedgehog antagonist. In preferred embodiments ,the unwanted cell proliferation is cancer or benign prostatic hyperplasia. Another aspect of the present invention involves measuring the levels of gli gene expression in order detn. the likelihood that a cancer will develop or to detn. a cancer treatment protocol. Another embodiment of the invention involves methods for using hedgehog antagonists to stimulate surfactant prodn. or lamellated body formation in lung cells, esp. the lung cells of premature infants. In other preferred embodiments, hedgehog antagonists are selected from small mols., hedgehog antibodies, antisense nucleic acids and ribozymes.

IT **334998-27-5**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

RN 334998-27-5 HCAPLUS
CN Butanamide, N-[1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-

pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl- (9CI) (CA INDEX NAME)

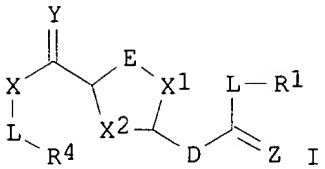


L12 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:293442 HCAPLUS
DOCUMENT NUMBER: 136:325823
TITLE: Preparation and formulation of proline derivatives as mediators of hedgehog signaling pathways for pharmaceutical and cosmetic uses
INVENTOR(S): Baxter, Anthony D.; Boyd, Edward A.; Guicherit, Oivin M.; Price, Stephen; Rubin, Lee D.
PATENT ASSIGNEE(S): Curis, Inc., USA
SOURCE: PCT Int. Appl., 230 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002030421	A2	20020418	WO 2001-US32054	20011012
WO 2002030421	A3	20020926		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002011713	A5	20020422	AU 2002-11713	20011012
US 2002165221	A1	20021107	US 2001-977096	20011012

PRIORITY APPLN. INFO.: US 2000-240536P P 20001013
US 2000-240564P P 20001013
WO 2001-US32054 W 20011012

OTHER SOURCE(S): MARPAT 136:325823
GI



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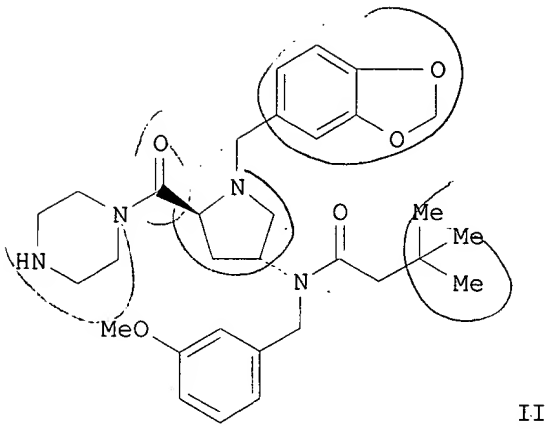


II

AB Proline-based compds. such as I [R1, R4 = H, alkyl, (CH2)n-(hetero)aryl (n = 0-5); L = null, -(CH2)n-, -alkenyl-, -alkynyl-, -(CH2)n-alkenyl-, -(CH2)n-alkynyl-, -(CH2)nO(CH2)p-, -(CH2)nNR8(CH2)p-, -(CH2)nS(CH2)p-, -(CH2)nalkenyl(CH2)p-, -(CH2)nalkynyl(CH2)p-, -O(CH2)n-,-NR8(CH2)n-, or -S(CH2)n- (R8 is any group given for R1 or two R8 together may form a 4- to 8-membered ring; p = 0-3); X, D = NR8, O, S, NR8NR8, ONR8, or a direct bond; Y, Z = O or S; E represents NR5, where R5 represents LR8 or an ammonium salt; X1, X2 = null, CH2 or CH2CH2] were prepd. for pharmaceutical and cosmetic use. Thus, proline deriv. II was prepd. via a multistep synthetic sequence which started with trans-4-hydroxy-L-proline, 3-methoxybenzaldehyde, piperonal, tert-butylacetyl chloride, and N-(tert-butoxycarbonyl)piperazine. The prepd. proline derivs. were tested for agonist activity for inhibiting aberrant growth states resulting from hedgehog gain-of-function, ptc loss-of-function or smoothened gain-of-function comprising contacting the cell with a hedgehog antagonist, such as a small mol., in a sufficient amt. to aberrant growth state, e.g., to agonize a normal ptc pathway or antagonize smoothened or hedgehog activity.

IT **334999-41-6P 334999-57-4P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. and formulation of proline derivs. for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

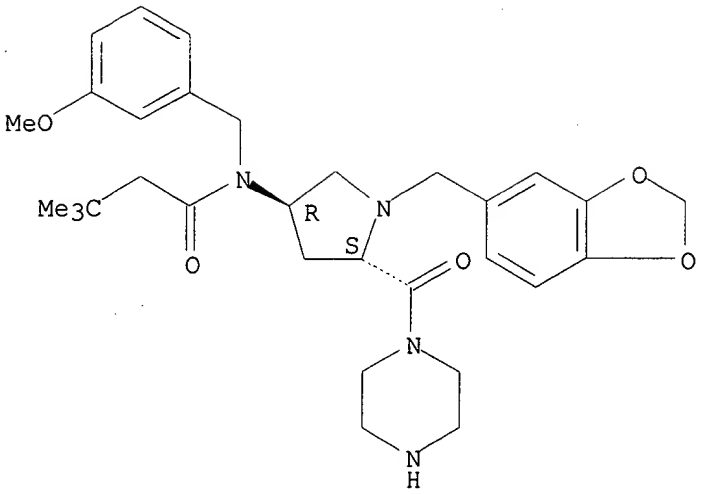
RN 334999-41-6 HCAPLUS

CN Butanamide, N-[(3R,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl-, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

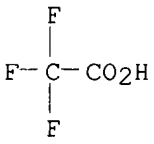
CRN 334998-37-7
CMF C31 H42 N4 O5

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

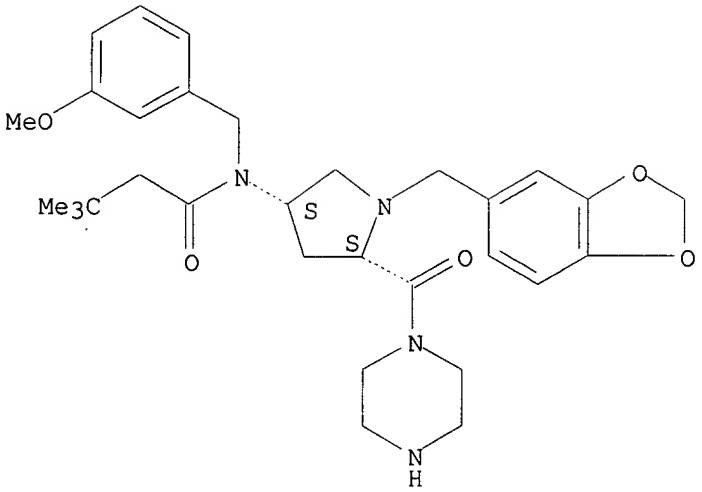


RN 334999-57-4 HCAPLUS
CN Butanamide, N-[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl-, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

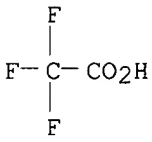
CRN 334998-36-6
CMF C31 H42 N4 O5

Absolute stereochemistry.



CM 2

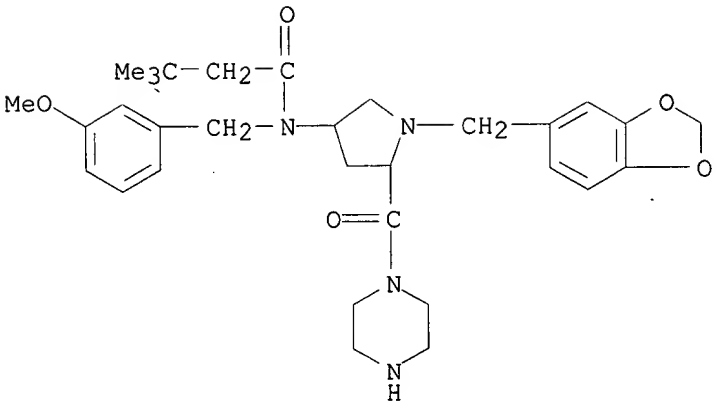
CRN 76-05-1
CMF C2 H F3 O2



IT **334998-27-5P 334998-36-6P 334998-37-7P**
334998-39-9P 334998-64-0P 334998-83-3P
334998-84-4P 334998-85-5P 334998-86-6P
334998-88-8P 334998-90-2P 334998-91-3P
334998-99-1P 334999-00-7P 334999-03-0P
334999-17-6P 334999-19-8P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and formulation of proline derivs. for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

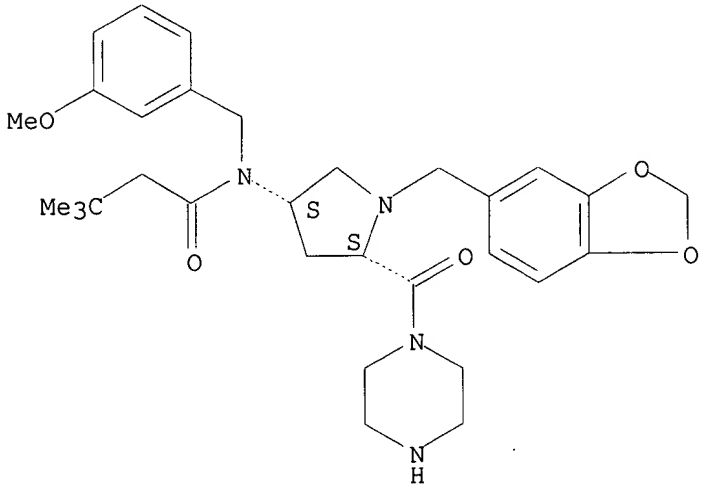
RN 334998-27-5 HCAPLUS

CN Butanamide, N-[1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl- (9CI) (CA INDEX NAME)



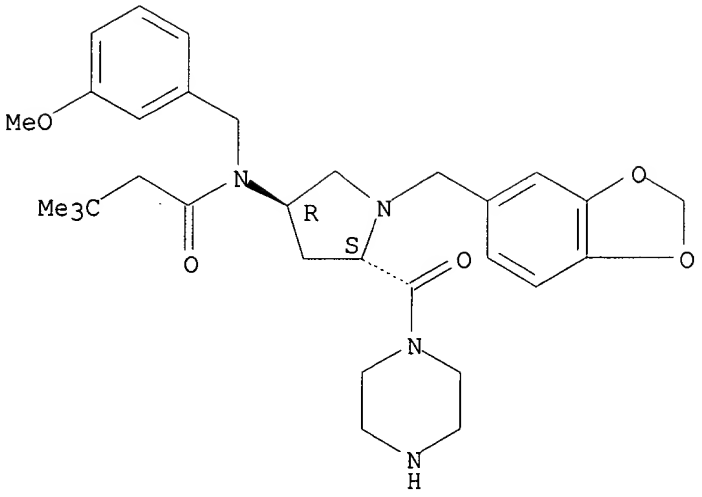
RN 334998-36-6 HCAPLUS
CN Butanamide, N-[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

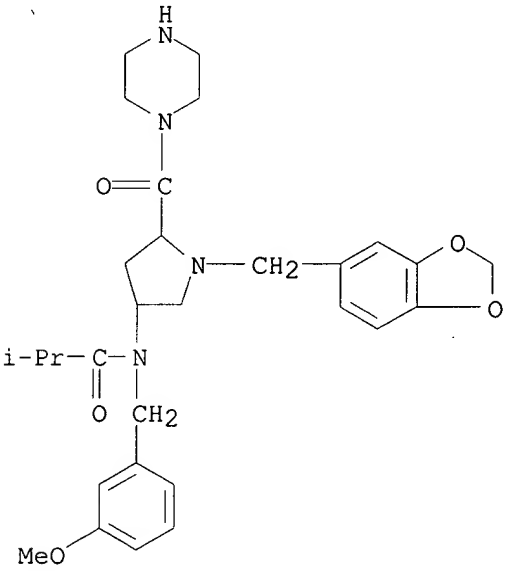


RN 334998-37-7 HCAPLUS
CN Butanamide, N-[(3R,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl- (9CI) (CA INDEX NAME)

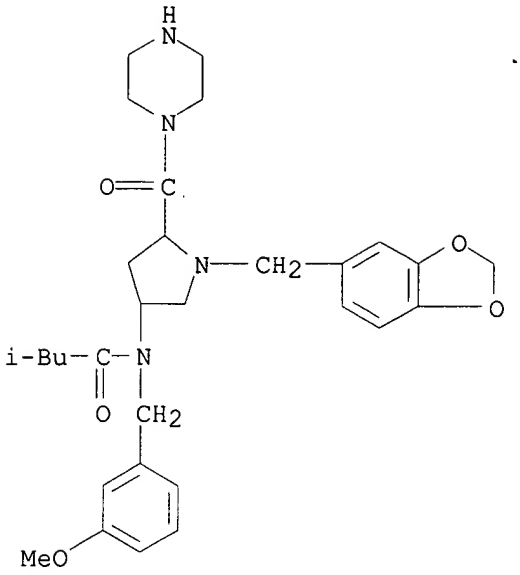
Absolute stereochemistry.



RN 334998-39-9 HCAPLUS
CN Propanamide, N-[1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-2-methyl- (9CI) (CA INDEX NAME)

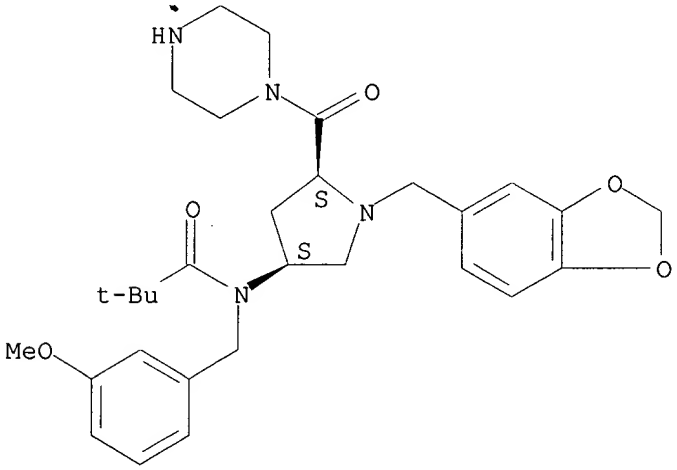


RN 334998-64-0 HCAPLUS
CN Butanamide, N-[1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3-methyl- (9CI) (CA INDEX NAME)



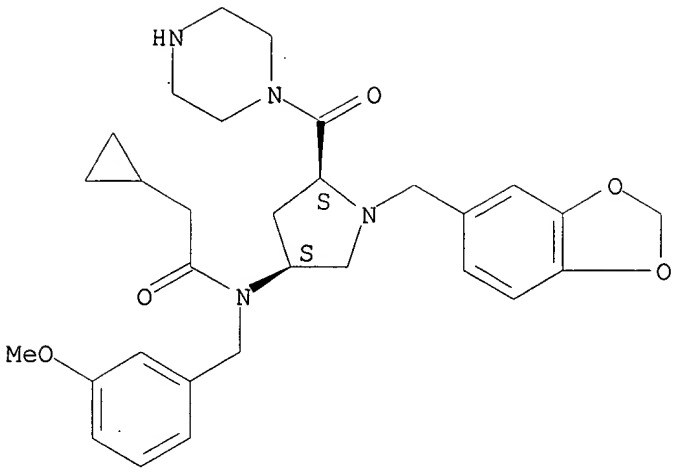
RN 334998-83-3 HCAPLUS
CN Propanamide, N-[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-2,2-dimethyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



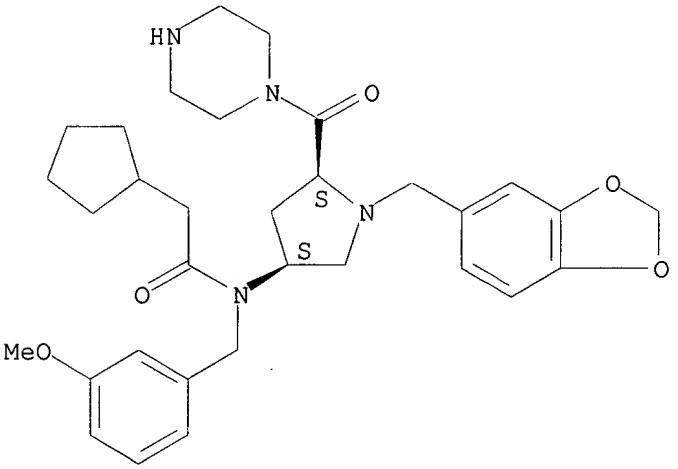
RN 334998-84-4 HCAPLUS
CN Cyclopropaneacetamide, N-[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



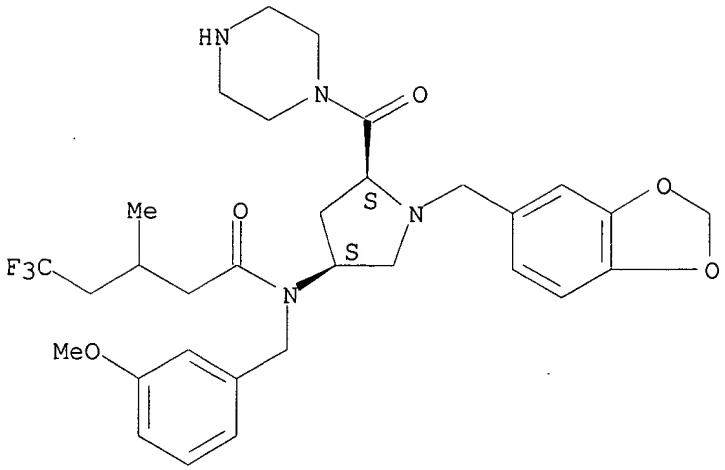
RN 334998-85-5 HCAPLUS
CN Cyclopentaneacetamide, N-[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



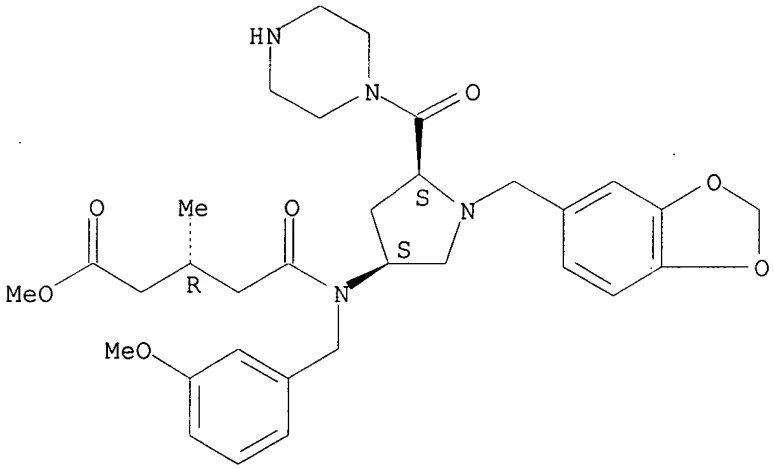
RN 334998-86-6 HCAPLUS
CN Pentanamide, N-[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-5,5,5-trifluoro-N-[(3-methoxyphenyl)methyl]-3-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



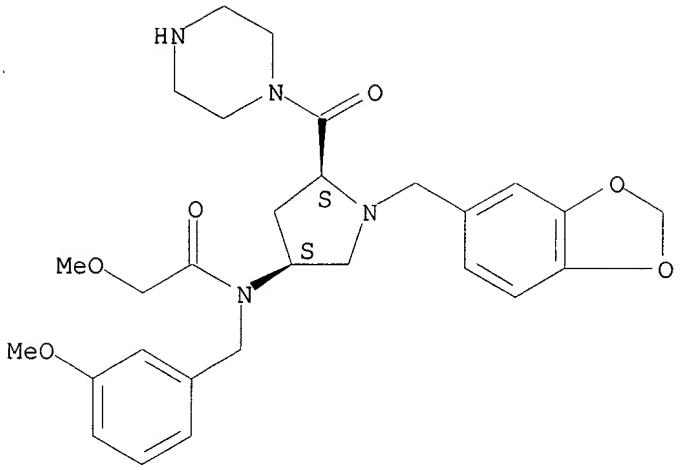
RN 334998-88-8 HCAPLUS
CN Pentanoic acid, 5-[[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl][(3-methoxyphenyl)methyl]amino]-3-methyl-5-oxo-, methyl ester, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



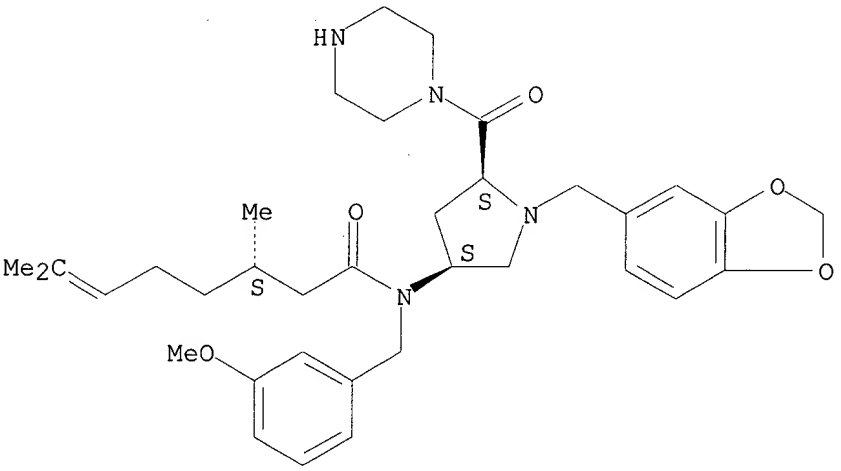
RN 334998-90-2 HCAPLUS
CN Acetamide, N-[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-2-methoxy-N-[(3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



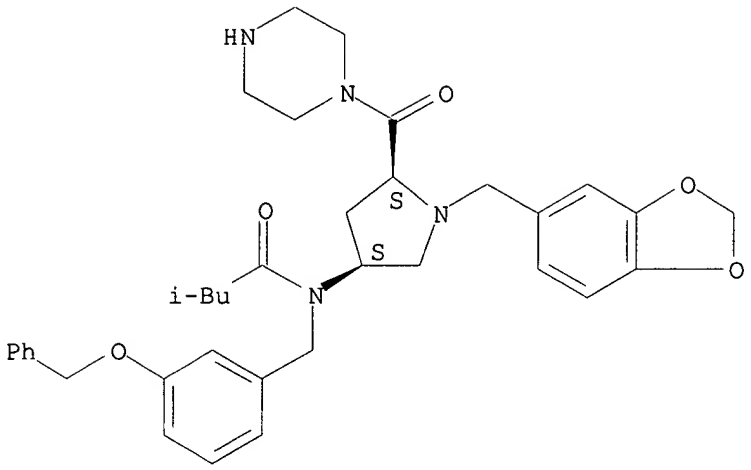
RN 334998-91-3 HCAPLUS
CN 6-Octenamide, N-[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,7-dimethyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



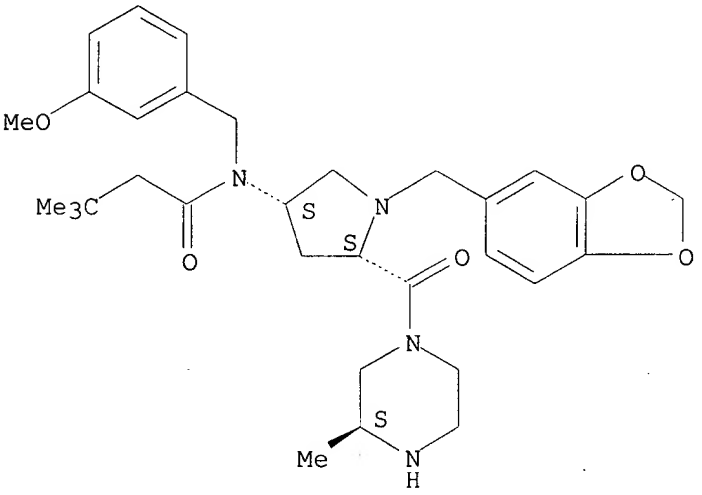
RN 334998-99-1 HCAPLUS
CN Butanamide, N-[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-3-methyl-N-[[3-(phenylmethoxy)phenyl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



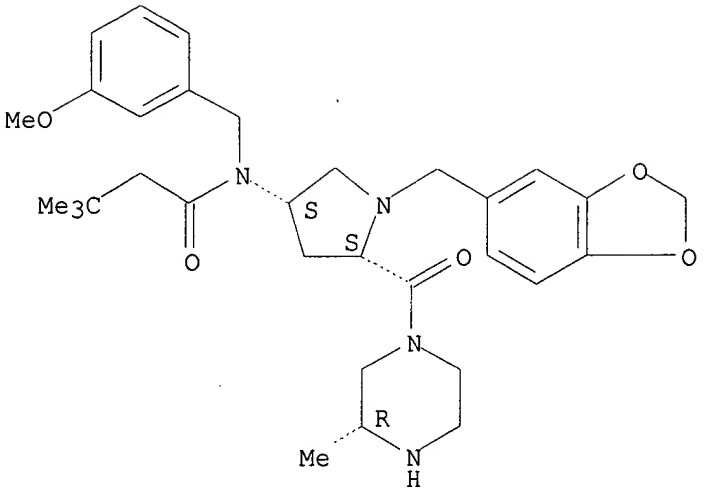
RN 334999-00-7 HCAPLUS
CN Butanamide, N-[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-[[(3S)-3-methyl-1-piperazinyl]carbonyl]-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



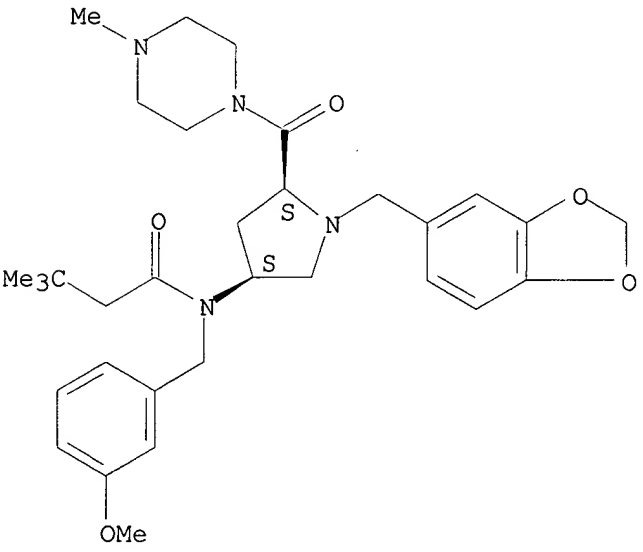
RN 334999-03-0 HCAPLUS
CN Butanamide, N-[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-[[(3R)-3-methyl-1-piperazinyl]carbonyl]-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



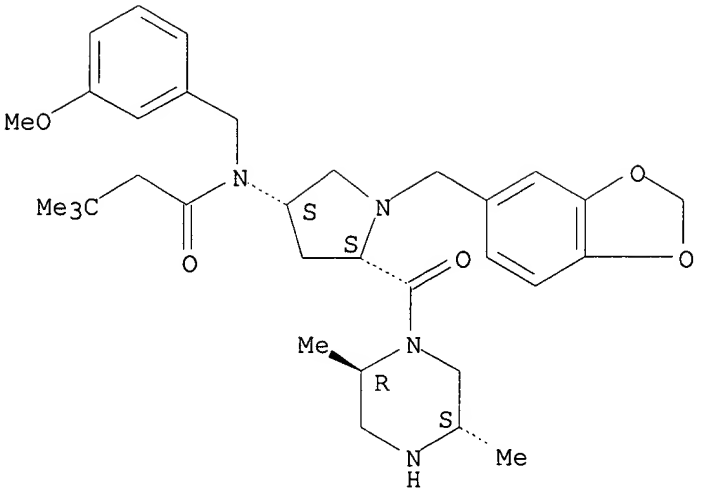
RN 334999-17-6 HCAPLUS
CN Butanamide, N-[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-[(4-methyl-1-piperazinyl)carbonyl]-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 334999-19-8 HCAPLUS
CN Butanamide, N-[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-[[(2R,5S)-2,5-dimethyl-1-piperazinyl]carbonyl]-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl- (9CI) (CA INDEX NAME)

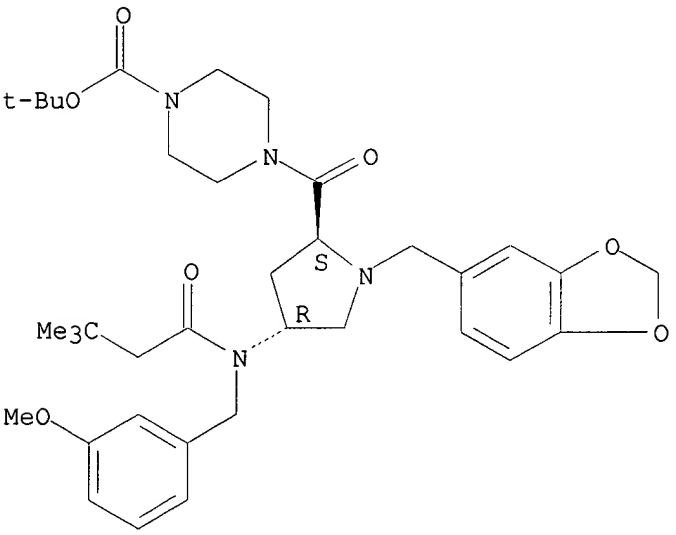
Absolute stereochemistry.



IT **334999-39-2P 334999-55-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and formulation of proline derivs. for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

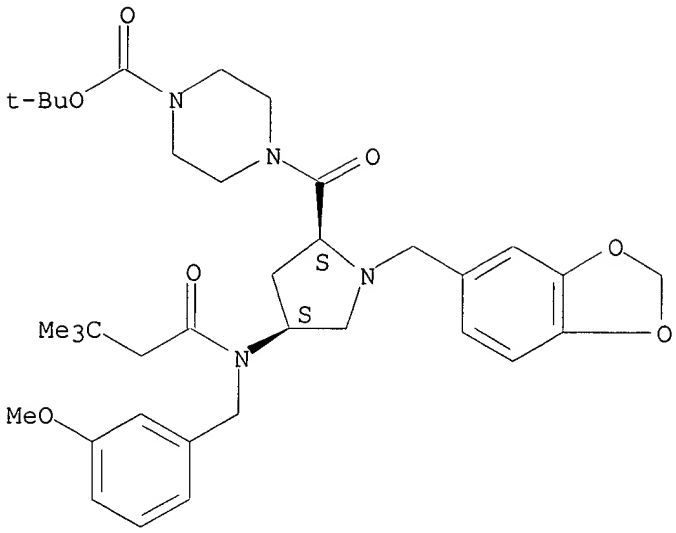
RN 334999-39-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-[[(2S,4R)-1-(1,3-benzodioxol-5-ylmethyl)-4-[(3,3-dimethyl-1-oxobutyl)[(3-methoxyphenyl)methyl]amino]-2-pyrrolidinyl]carbonyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 334999-55-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-[[(2S,4S)-1-(1,3-benzodioxol-5-ylmethyl)-4-[(3,3-dimethyl-1-oxobutyl)[(3-methoxyphenyl)methyl]amino]-2-pyrrolidinyl]carbonyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L12 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:283777 HCAPLUS
DOCUMENT NUMBER: 134:311102
TITLE: Preparation and formulation of heterocycles as mediators of hedgehog signaling pathways for pharmaceutical and cosmetic uses
INVENTOR(S): Baxter, Anthony David; Boyd, Edward Andrew; Guicherit, Oivin M.; Price, Stephen; Rubin, Lee
PATENT ASSIGNEE(S): Curis, Inc., USA
SOURCE: PCT Int. Appl., 219 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001026644	A2	20010419	WO 2000-US28579	20001013
WO 2001026644	A3	20020418		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1227805	A2	20020807	EP 2000-978225	20001013
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JP 2003511411	T2	20030325	JP 2001-529434	20001013

PRIORITY APPLN. INFO.: US 1999-159417P P 19991014
US 2000-196543P P 20000411
WO 2000-US28579 W 20001013

OTHER SOURCE(S): MARPAT 134:311102
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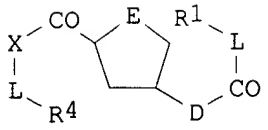
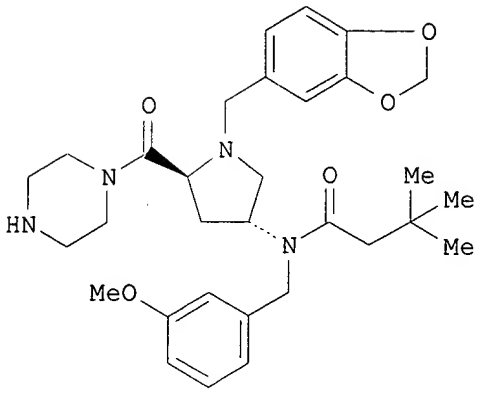


I



II

AB Heterocycles, such as I [E = O, S, NR; D, X = NR2, O, S, bond, etc.; L = linking group, such as alkylene, alkenylene, alkynylene; XL = piperazin-1,4-diyl, etc.; R, R1, R2 = H, alkyl, acyl, arylalkyl, heteroarylalkyl, etc.], were prepd. for pharmaceutical and cosmetic use. Thus, pyrrolidine II was prepd. via a multistep synthetic sequence which started with trans-4-hydroxy-L-proline, 3-methoxybenzaldehyde, piperonal, tert-butylacetyl chloride, and N-(tert-butoxycarbonyl)piperazine. The prepd. pyrrolidines were tested for agonist activity for inhibiting aberrant growth states resulting from hedgehog gain-of-function, ptc loss-of-function or smoothened gain-of-function comprising contacting the cell with a hedgehog antagonist, such as a small mol., in a sufficient amt. to aberrant growth state, e.g., to agonize a normal ptc pathway or antagonize smoothened or hedgehog activity.

IT **334999-41-6P 334999-57-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. and formulation of pyrrolidines for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

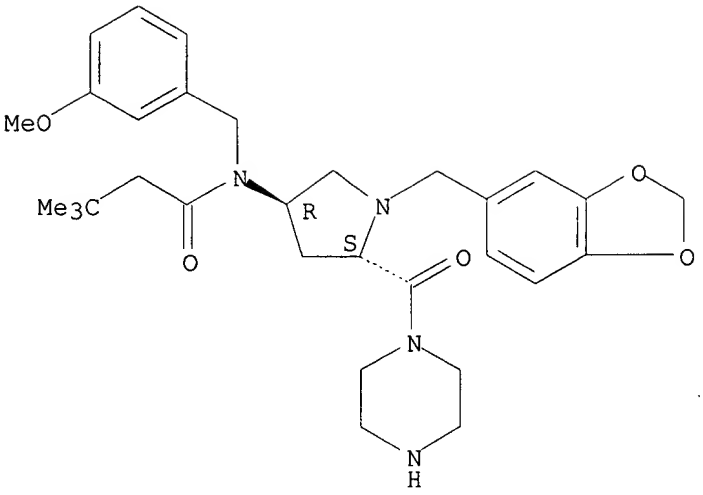
RN 334999-41-6 HCAPLUS

CN Butanamide, N-[(3R,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl-, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

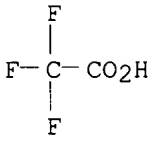
CRN 334998-37-7
CMF C31 H42 N4 O5

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

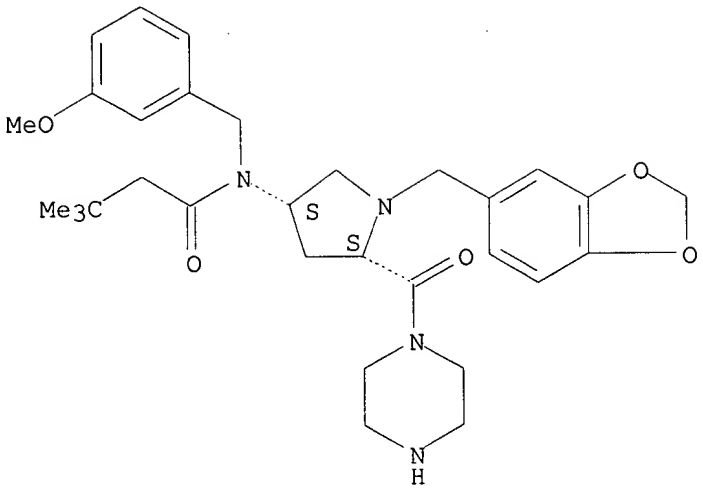


RN 334999-57-4 HCAPLUS
CN Butanamide, N-[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl-, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

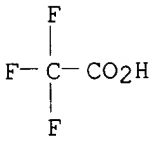
CRN 334998-36-6
CMF C31 H42 N4 O5

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2



IT **334998-27-5P 334998-36-6P 334998-37-7P**
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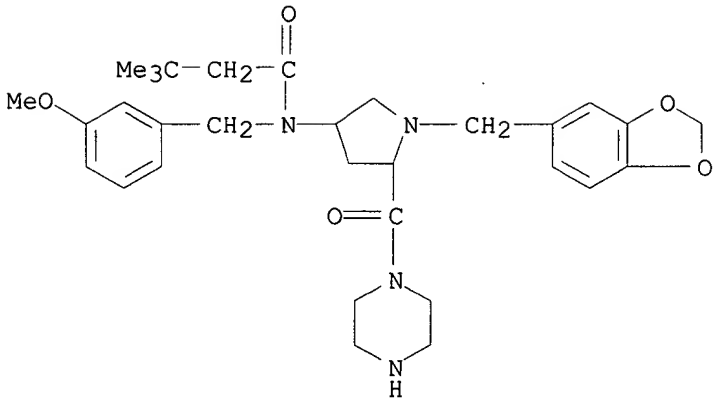
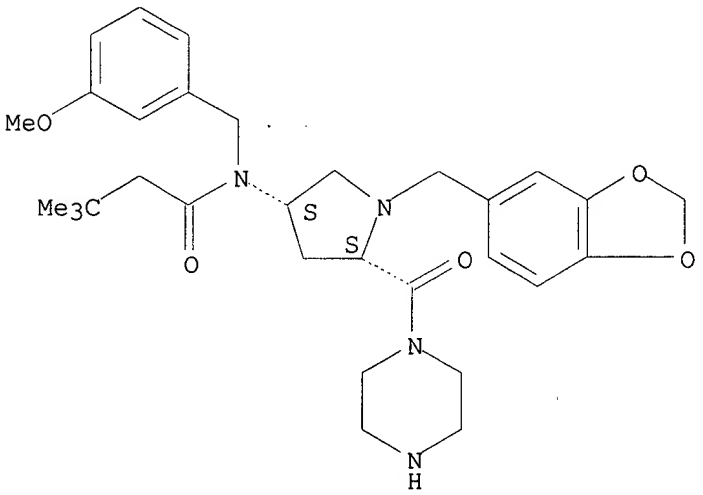
334999-17-6P 334999-19-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and formulation of pyrrolidines for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

RN 334998-27-5 HCAPLUS
CN Butanamide, N-[1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl- (9CI) (CA INDEX NAME)



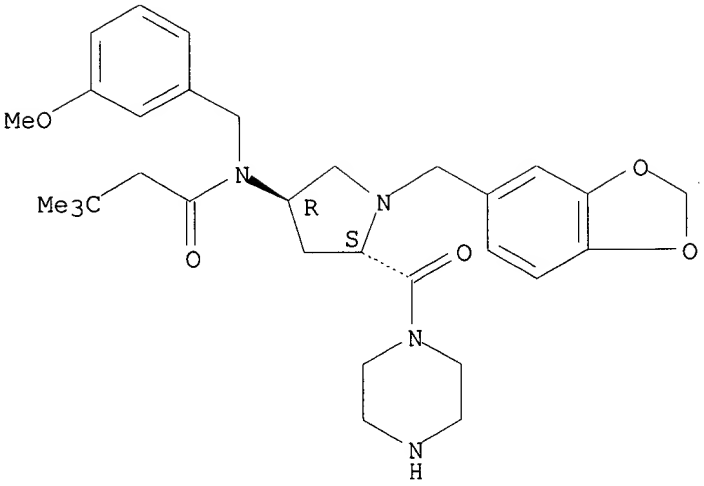
RN 334998-36-6 HCAPLUS
CN Butanamide, N-[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

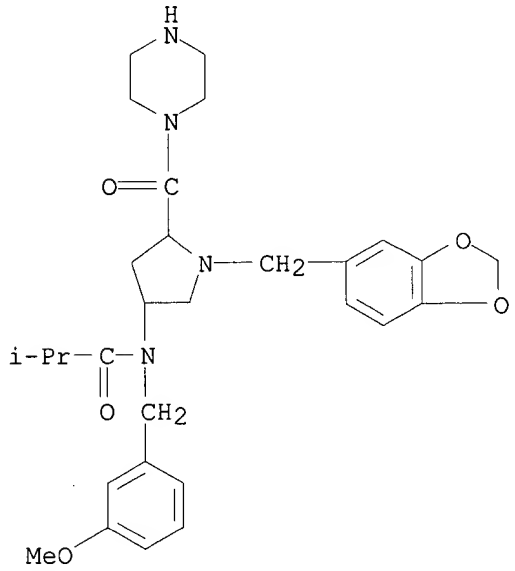


RN 334998-37-7 HCAPLUS
CN Butanamide, N-[(3R,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl- (9CI) (CA INDEX NAME)

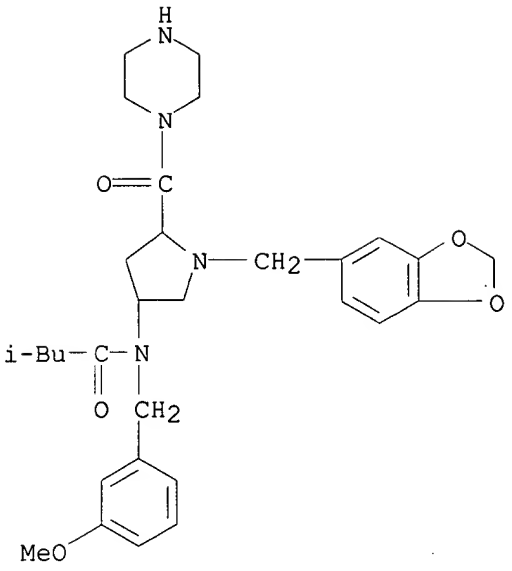
Absolute stereochemistry.



RN 334998-39-9 HCAPLUS
CN Propanamide, N-[1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-2-methyl- (9CI) (CA INDEX NAME)

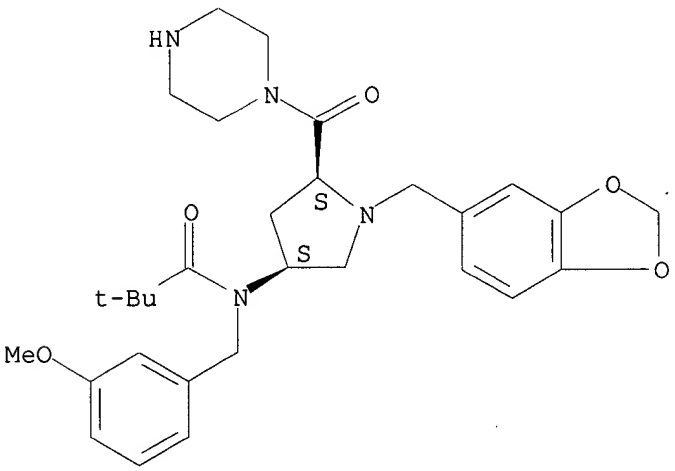


RN 334998-64-0 HCAPLUS
CN Butanamide, N-[1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3-methyl- (9CI) (CA INDEX NAME)



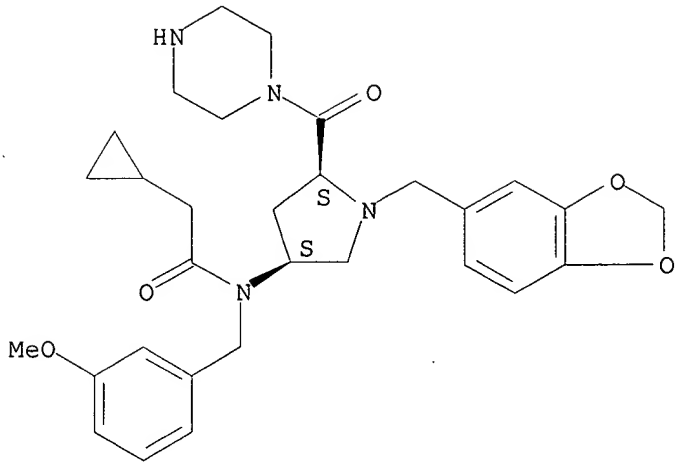
RN 334998-83-3 HCAPLUS
CN Propanamide, N-[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-2,2-dimethyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



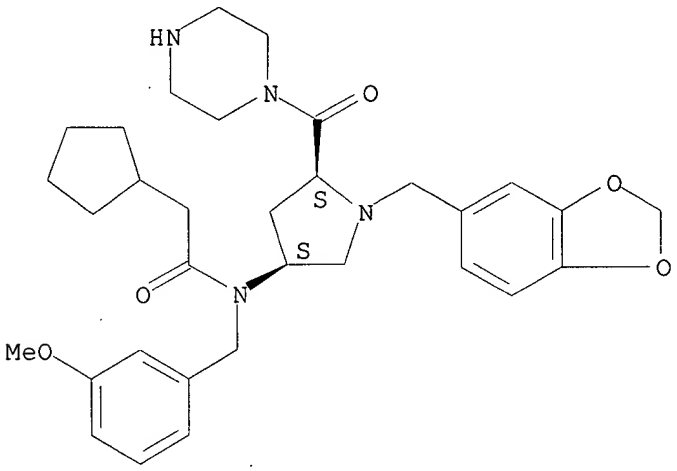
RN 334998-84-4 HCAPLUS
CN Cyclopropaneacetamide, N-[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



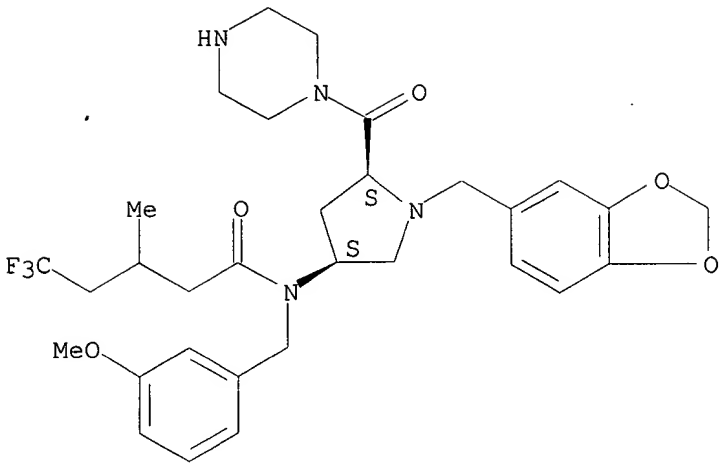
RN 334998-85-5 HCAPLUS
CN Cyclopentaneacetamide, N-[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



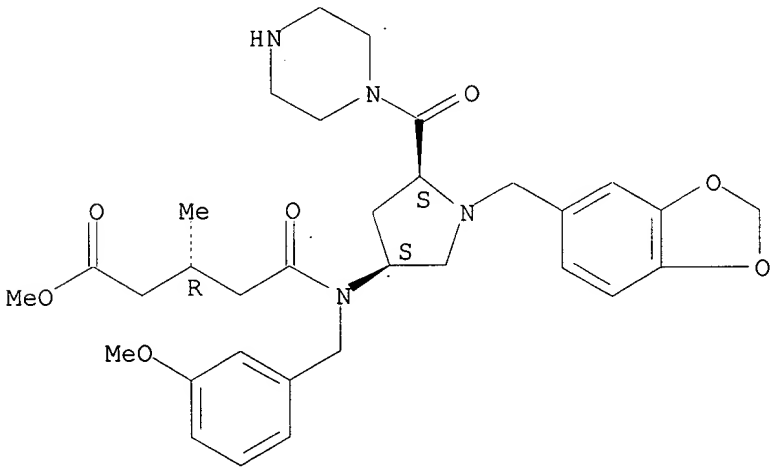
RN 334998-86-6 HCAPLUS
CN Pentanamide, N-[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-5,5,5-trifluoro-N-[(3-methoxyphenyl)methyl]-3-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



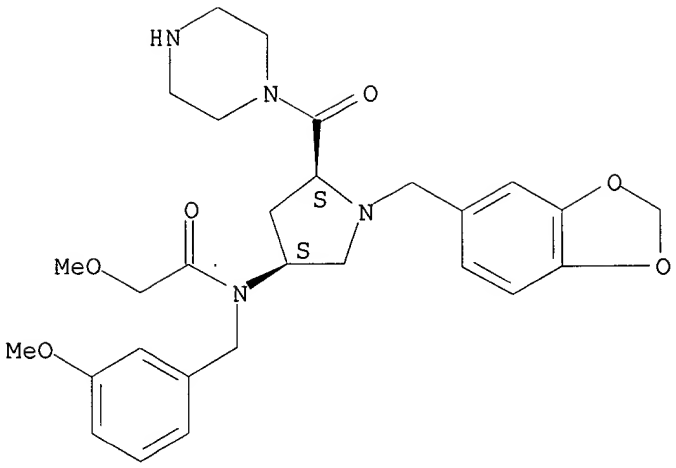
RN 334998-88-8 HCAPLUS
CN Pentanoic acid, 5-[[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl][(3-methoxyphenyl)methyl]amino]-3-methyl-5-oxo-, methyl ester, (3R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



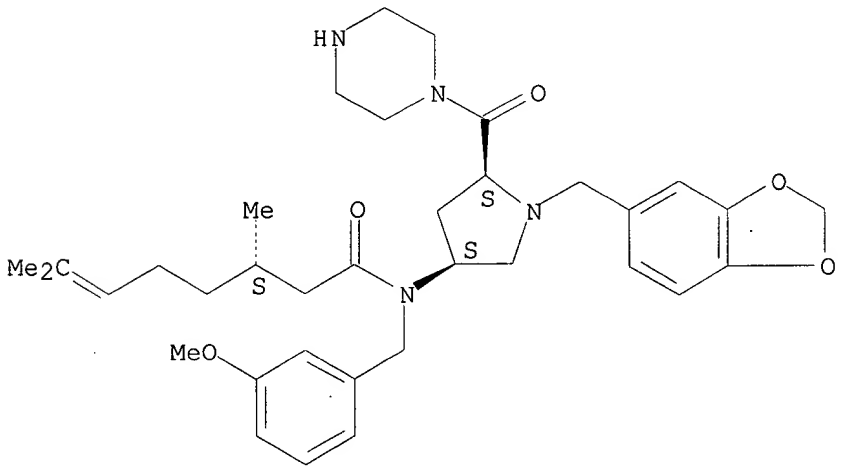
RN 334998-90-2 HCAPLUS
CN Acetamide, N-[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-2-methoxy-N-[(3-methoxyphenyl)methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



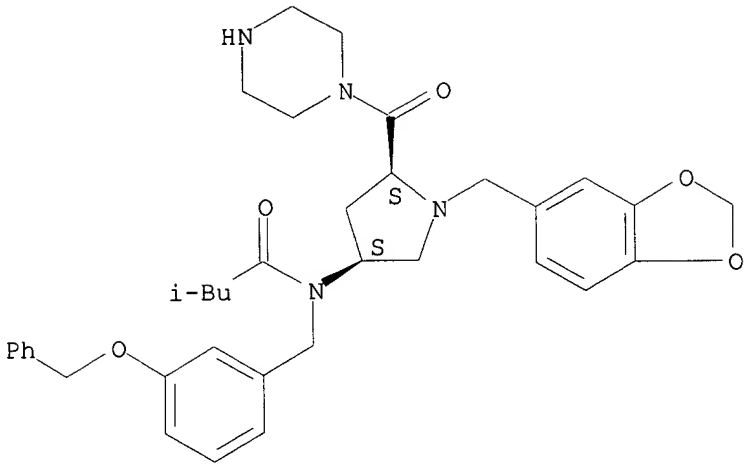
RN 334998-91-3 HCAPLUS
CN 6-Octenamide, N-[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,7-dimethyl-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



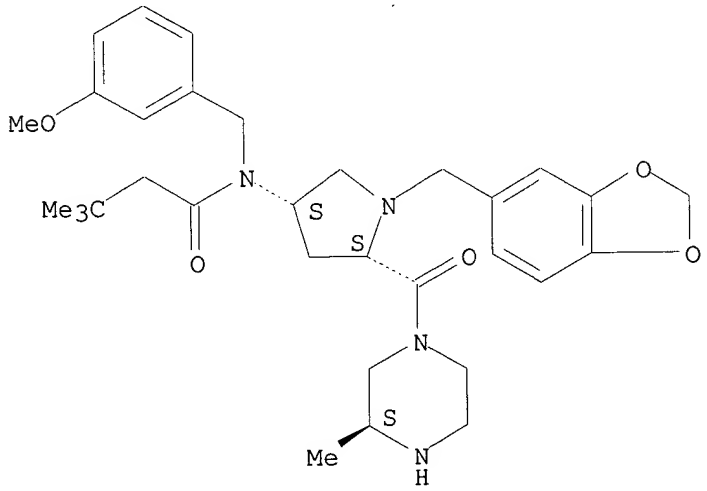
RN 334998-99-1 HCAPLUS
CN Butanamide, N-[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-3-methyl-N-[[3-(phenylmethoxy)phenyl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 334999-00-7 HCAPLUS
CN Butanamide, N-[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-[[(3S)-3-methyl-1-piperazinyl]carbonyl]-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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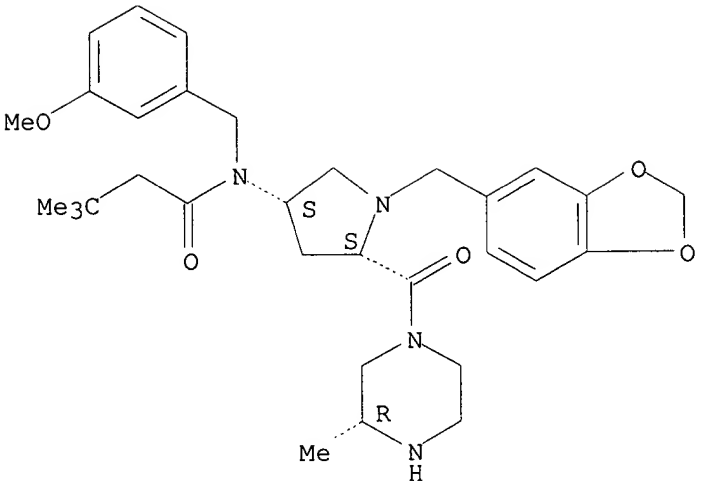
Absolute stereochemistry.



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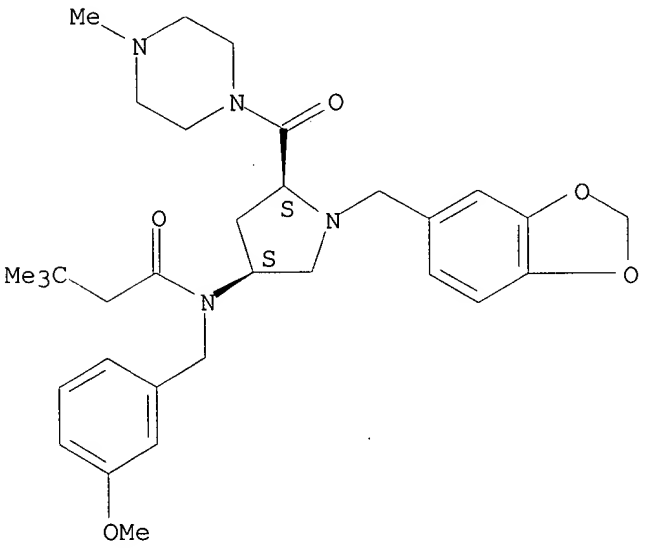
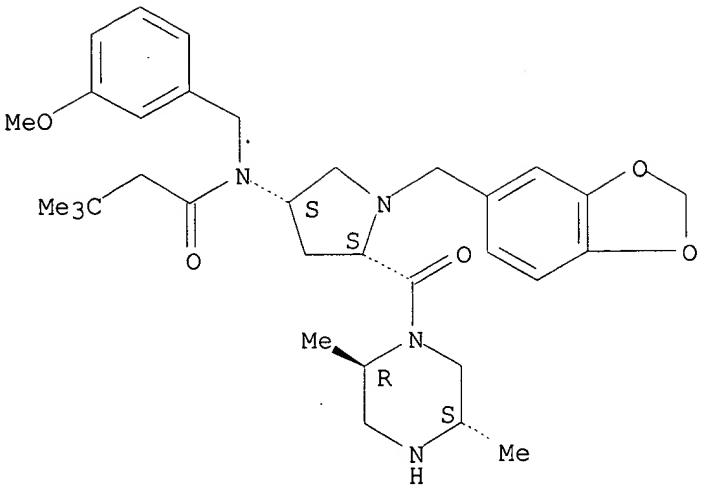
CN Butanamide, N-[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-[(4-methyl-1-piperazinyl)carbonyl]-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 334999-19-8 HCAPLUS
CN Butanamide, N-[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-[[(2R,5S)-2,5-dimethyl-1-piperazinyl]carbonyl]-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl- (9CI) (CA INDEX NAME)

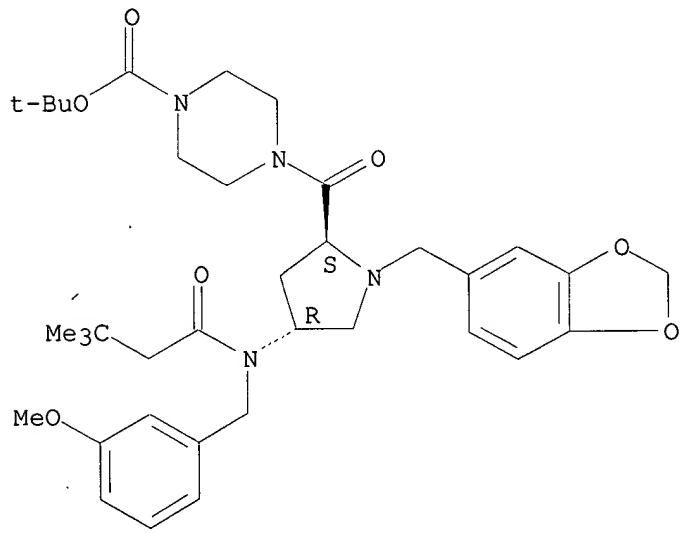
Absolute stereochemistry.



IT **334999-39-2P 334999-55-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and formulation of pyrrolidines for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

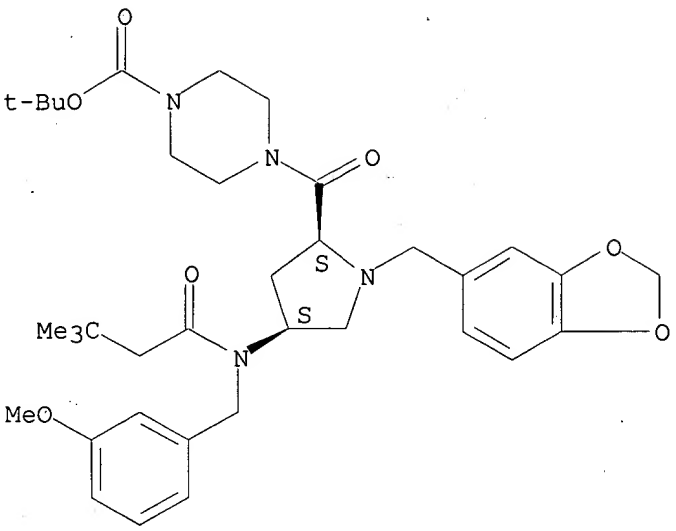
RN 334999-39-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-[[(2S,4R)-1-(1,3-benzodioxol-5-ylmethyl)-4-[(3,3-dimethyl-1-oxobutyl)[(3-methoxyphenyl)methyl]amino]-2-pyrrolidinyl]carbonyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 334999-55-2 HCAPLUS
CN 1-Piperazinecarboxylic acid, 4-[[(2S,4S)-1-(1,3-benzodioxol-5-ylmethyl)-4-[(3,3-dimethyl-1-oxobutyl)[(3-methoxyphenyl)methyl]amino]-2-pyrrolidinyl]carbonyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.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FILE COVERS 1907 - 18 Apr 2003  VOL 138 ISS 17
FILE LAST UPDATED: 17 Apr 2003  (20030417/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


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L13        2949 SEA FILE=REGISTRY ABB=ON  PLU=ON  L9 NOT L11
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L17          35 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L14 AND (?PHARM? OR ?MEDIC?
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L18  ANSWER 1 OF 33  HCAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2003:242278  HCAPLUS
TITLE:                    Preparation of cyclic hydroxamic acids as inhibitors
                          of matrix metalloproteinases and/or TNF-.alpha.
                          converting enzyme for treatment of inflammatory
                          disorders
INVENTOR(S):              Ott, Gregory; Chen, Xiao-Tao; Duan, Jingwu; Lu,
                          Zhonghui
PATENT ASSIGNEE(S):       Bristol-Myers Squibb Company, USA
SOURCE:                   PCT Int. Appl., 344 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:
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PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003024899	A2	20030327	WO 2002-US29685	20020916

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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-322630P P 20010917

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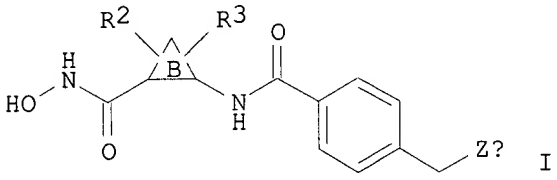

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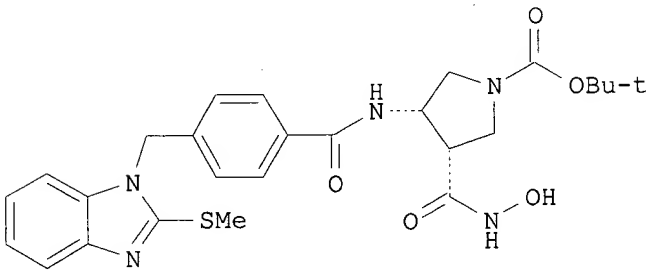

II

AB Title compds. I [wherein ring B = (un)substituted 4-7 membered (hetero)cyclic ring contg. 0-2 O, N, NR1, or SOp atoms and 0-3 carbonyl groups; R1 and R2 = independently Q, alk(en/yn)ylene-Q, or (un)substituted alkylene-Q interrupted by O, NRa, CO, CO2, CONRa, NRaCO, NRaCO2, NRaCONRa, SOp, NRaSO2, or SO2NRa; or R1 = (un)substituted alkylene-Q interrupted by OCO, OCO2, or OCONRa; Q = H or (un)substituted (hetero)cyclyl; R3 = Q1, Cl, F, alk(en/yn)ylene-Q1, or (un)substituted alkylene-Q1 interrupted by O, NR1, NRaCO, CONRa, CO, CO2, SOp, or SO2NRa; Q1 = H or (un)substituted Ph, naphthyl, or heterocyclyl; Za = (un)substituted benzimidazolyl, indolyl, imidazopyridinyl, pyrazolylpyridinyl, benzofuranyl, benzothiazinyl, quinolinyl, etc.; Ra = independently H, alkyl, Ph, or benzyl; p = 0-2; or stereoisomers or **pharmaceutically** acceptable salts thereof] were prepd. as inhibitors of matrix metalloproteinases (MMP), TNF-a converting enzyme (TACE), aggrecanase, or a combination thereof. For example, reaction of benzyl Me maleate with paraformaldehyde and glycine gave benzyl Me (cis)-3,4-pyrrolidinedicarboxlyate (100%). BOC-protection (64%), debenzylation (96%), resoln. of the (3S,4S)-isomer with (S)-.alpha.-methylbenzylamine, conversion to the carbamate with DPPA and PhCH2OH (76%), and Pd catalyzed hydrogenation (100%) provided Me (3S,4S)-4-amino-1-(tert-butoxycarbonyl)-3-pyrrolidinecarboxylate. Coupling of the amine with 4-[(2-methylthio-1H-benzimidazol-1-yl)methyl]benzoic acid (prepn. given) afforded the amide (99%), which was treated with NH2OH.bul.HCl/MeONa to give the hydroxamic acid (3S,4S)-II

(33%). A no. of the compds. of the invention inhibited MMP-1, 2, 3, 7, 8, 9, 10, 12, 13, 14, 15, and/or 16 with Ki values of .ltoreq. 10 .mu.M. Thus, I are useful for the treatment of a wide variety of inflammatory disorders (no data).

IT **503165-90-0P 503166-11-8P 503166-20-9P**
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503169-60-6P 503170-36-3P 503170-64-7P
503172-29-0P 503172-34-7P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(MMR and/or TACE inhibitor; prepn. of cyclic hydroxamic acids as MMP and/or TACE inhibitors for treatment of inflammatory disorders)

IT **503165-97-7P 503165-98-8P 503166-01-6P**
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503169-63-9P 503169-64-0P 503169-65-1P
503169-70-8P 503169-71-9P 503169-73-1P
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503169-90-2P 503169-91-3P 503169-93-5P
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503169-99-1P 503170-00-1P 503170-02-3P
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503170-17-0P 503170-18-1P 503170-20-5P
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503170-35-2P 503170-38-5P 503170-39-6P
503170-40-9P 503170-44-3P 503170-45-4P
503170-48-7P 503170-49-8P 503170-51-2P
503170-52-3P 503170-63-6P 503170-66-9P
503170-67-0P 503170-68-1P 503170-71-6P
503170-82-9P 503170-83-0P 503170-91-0P
503170-92-1P 503171-00-4P 503171-01-5P
503171-07-1P 503171-08-2P 503171-30-0P
503171-31-1P 503172-30-3P 503172-31-4P
503172-35-8P 503172-36-9P 503172-95-0P
503172-96-1P 503172-97-2P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(MMR and/or TACE inhibitor; prepn. of cyclic hydroxamic acids as MMP and/or TACE inhibitors for treatment of inflammatory disorders)

IT 362489-81-4P 362490-80-0P 503165-95-5P
503165-96-6P 503165-99-9P 503166-00-5P
503166-02-7P 503166-04-9P 503166-10-7P
503166-14-1P 503166-21-0P 503166-24-3P
503166-39-0P 503166-42-5P 503166-70-9P
503166-73-2P 503166-81-2P 503166-84-5P
503167-10-0P 503167-14-4P 503167-17-7P
503167-21-3P 503167-28-0P 503167-32-6P
503167-36-0P 503167-40-6P 503167-66-6P
503167-67-7P 503167-68-8P 503167-76-8P
503167-80-4P 503167-84-8P 503167-85-9P
503167-92-8P 503167-96-2P 503168-33-0P
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503169-29-7P 503169-32-2P 503169-50-4P
503169-58-2P 503169-62-8P 503169-68-4P
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503170-43-2P 503170-47-6P 503170-50-1P
503170-53-4P 503170-65-8P 503170-69-2P
503170-70-5P 503170-72-7P 503170-84-1P
503170-93-2P 503171-02-6P 503171-03-7P
503171-09-3P 503171-10-6P 503171-36-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; prepn. of cyclic hydroxamic acids as MMP and/or TACE inhibitors for treatment of inflammatory disorders)

IT **503169-19-5**
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of cyclic hydroxamic acids as MMP and/or TACE inhibitors for treatment of inflammatory disorders)

L18 ANSWER 2 OF 33 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:242180 HCAPLUS
TITLE: Preparation of .beta.-peptides in method for delivery of molecules to intracellular targets
INVENTOR(S): Gellman, Samuel H.; Umezawa, Naoki; Gelman, Michael A.; Raines, Ronald T.; Potocky, Terra
PATENT ASSIGNEE(S): Wisconsin Alumni Research Foundation, USA
SOURCE: PCT Int. Appl., 111 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003024477	A1	20030327	WO 2002-US29568	20020918

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-323512P P 20010918

AB Disclosed are .beta.-peptides and .beta.-peptide conjugates that are capable of diffusing or otherwise being transported across the cell membranes of living cells. The .beta.-peptides contain at least six .beta.-amino acid residues, at least six of which are preferably .beta.3-homoarginine residues. When **pharmacol**.-active agents are conjugated to these types of .beta.-peptides, the resulting conjugates (also disclosed) are also capable of diffusing or otherwise being transported across the cell membranes of living cells, including mammalian cells. The examples include the synthesis of cyclohexyl-contg. .beta.-amino acids and the soln.-phase synthesis of a .beta.-peptide chain contg. alternating residues of unsubstituted cyclohexane rings and amino-substituted cyclohexane rings.

IT **267230-37-5P 267230-38-6P**
RL: BPN (Biosynthetic preparation); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of .beta.-peptides in method for delivery of mols. to intracellular targets)

IT **267230-39-7P**
RL: BPN (Biosynthetic preparation); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of .beta.-peptides in method for delivery of mols. to intracellular targets)

IT **267230-42-2P 267230-43-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of .beta.-peptides in method for delivery of mols. to intracellular targets)

IT **267230-44-4P 267230-53-5P 267230-54-6P**

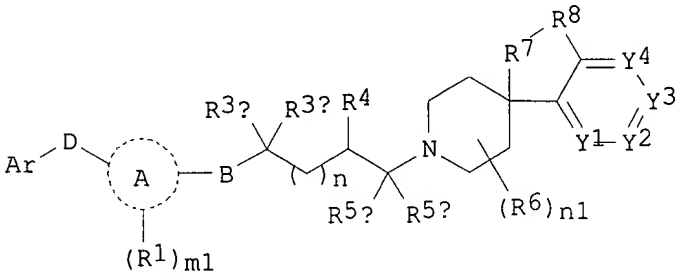
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of .beta.-peptides in method for delivery of mols. to intracellular targets)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 3 OF 33 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:849596 HCAPLUS
DOCUMENT NUMBER: 137:370353
TITLE: Preparation of spiropiperidine derivatives, nociceptin receptor antagonists containing the same as the active ingredient, and **medicinal** compositions
INVENTOR(S): Sagara, Takeshi; Itoh, Satoru; Nakashima, Hiroshi; Goto, Yasuhiro; Shimizu, Atsushi; Iwasawa, Yoshikazu; Okamoto, Osamu
PATENT ASSIGNEE(S): Banyu Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 187 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002088089	A1	20021107	WO 2002-JP3878	20020418

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: JP 2001-121543 A 20010419
OTHER SOURCE(S): MARPAT 137:370353
GI



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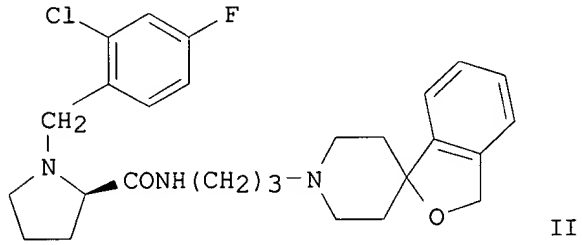


II

AB Spiropiperidine derivs. typified by compds. represented by the general formula (I) or **pharmacol**. acceptable salts thereof [wherein the ring A = 3- to 6-membered monocyclic arom. or aliph. ring optionally contg. 1 or .gtoreq.2 heteroatoms selected from N, O, and S; B = CONH, NHCO; D = a single bond, O, S, CO, (un)substituted CH2 or CH2CH2; R1 = HO, halo, mono or di(lower alkyl)amino, lower alkylsulfonyl, lower alkylsulfinyl, optionally F-substituted lower alkoxy, lower alkylcarbonyloxy, lower alkylcarbonylamino, (un)substituted lower alkyl; m1 = an integer of 0-4; n = 0,1; R3a, R3b, R5a, R5b = H, halo, C1-3 alkyl, C1-3 haloalkyl; R4 = H, halo, HO, C1-3 alkyl, C1-3 haloalkyl; or R5a and R5b together form CH2, CH2CH2, or (CH2)3; R6 = halo, C1-3 alkyl; m = an integer of 0-8; R7, R8 = O, CH2; or R7 and R8 together form CH:CH; provided that R7 and R8 are not simultaneously O; Ar = (un)substituted mono- or bicyclic aryl or heteroaryl; Y1-Y4 = (un)substituted CH, N; provided that .gtoreq.2 of Y1-Y4 are not simultaneously N]. These compds. have an antagonistic effect on the binding of nociceptin to a nociceptin receptor ORL1 at an extremely low concn., which makes them useful as analgesics for cancer pain and diseases in assocd. with pain, antagonists to narcotic analgesic-tolerance, antagonists to narcotic analgesic -addiction or withdrawal syndrome, analgesic potentiators, antiobesity agents, brain function improving agents, and remedies for Alzheimer's disease, dementia, schizophrenia, Parkinson's disease, Huntington's chorea, depression, diabetes insipidus, polyuria, and hypotension. Thus, to a soln. of N-[3-[spiro[isobenzofuran-1(3H),4'-piperidine]-1-yl]propyl]-D-prolinamide dihydrochloride in DMF were added 2-chloro-4-fluorobenzaldehyde and sodium triacetoxyborohydride successively and stirred at room temp. for 4 h to give 1-(2-chloro-4-fluorobenzyl)-N-[3-spiro[isobenzofuran-1(3H),4'-piperidine]-1-ylpropyl]-D-prolinamide (II). II showed IC50 of 0.043 nM for inhibiting the binding of [125I]Tyr14-nociceptin to a membrane prepn. obtained from CHO cells transfected with human nociceptin gene.

IT **475151-05-4P 475151-10-1P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of spiropiperidine derivs. as nociceptin receptor antagonists, analgesics, antiobesity agents, brain function improvers, or remedies for neurodegenerative diseases, diabetes insipidus, polyuria, hypotension, or depression)

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 4 OF 33 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:833305 HCAPLUS
DOCUMENT NUMBER: 137:333131
TITLE: Methods of treating multiple myeloma and myeloma-induced bone resorption using integrin antagonists
INVENTOR(S): Mundy, Gregory R.; Yoneda, Toshiyuki
PATENT ASSIGNEE(S): Board of Regents, The University of Texas System, USA
SOURCE: U.S. Pat. Appl. Publ., 64 pp., Cont.-in-part of U.S. Ser. No. 943,659.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002159998	A1	20021031	US 2002-86217	20020221
WO 2000015247	A2	20000323	WO 1999-US21170	19990913

WO 2000015247 A3 20000525
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
US 2002022028 A1 20020221 US 2001-805840 20010313
US 2002041874 A1 20020411 US 2001-943659 20010831
PRIORITY APPLN. INFO.: US 1998-100182P P 19980914
WO 1999-US21170 A1 19990913
US 2001-805840 A2 20010313
US 2001-943659 A2 20010831

AB Antagonists of .alpha.4 integrin/.alpha.4 integrin ligand adhesion, which inhibit the biol. effects of such adhesion are described and methods for their use are detailed. Such antagonists are useful in suppressing bone destruction assocd. with multiple myeloma. The homing of multiple myeloma cells to bone marrow and their .alpha.4 integrin-dependent release of bone-resorbing factors, resulting in bone destruction in patients with multiple myeloma, is inhibited.

IT **410084-86-5P**, BIO 8809
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(BIO 8809; treatment of multiple myeloma and myeloma-induced bone resorption using integrin antagonists and **chemotherapeutic** agents)

IT **409325-34-4P 409325-35-5P 409325-36-6P 409325-37-7P 409325-38-8P 473806-21-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(treatment of multiple myeloma and myeloma-induced bone resorption using integrin antagonists and **chemotherapeutic** agents)

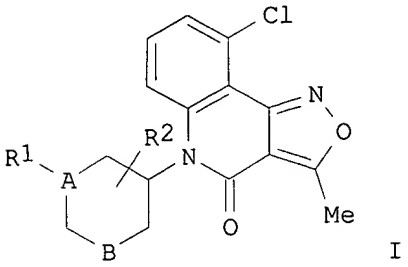
IT **410084-88-7P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(treatment of multiple myeloma and myeloma-induced bone resorption using integrin antagonists and **chemotherapeutic** agents)

L18 ANSWER 5 OF 33 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:793631 HCAPLUS
DOCUMENT NUMBER: 137:310905
TITLE: Preparation of piperidinyl-substituted isoxazolo[4,3-c]quinolinones for inhibiting MRP1
INVENTOR(S): Cohen, Jeffrey Daniel; Jungheim, Louis Nickolaus; Muehl, Brian Stephen; Thrasher, Kenneth Jeff
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002081480	A1	20021017	WO 2002-US6662	20020327

W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK,

SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW,
AM, AZ, BY, KG
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 2001-282642P P 20010409
OTHER SOURCE(S): MARPAT 137:310905
GI



I

AB The title compds. [I; B is either NR3 or CH2 and A is either CH or N; provide that when B = NR3, A = CH and when B = CH2, A = N; R1 = H, alkyl, (CH2)nCOR4, etc.; n = 0-2; R2 = H, O; R4 = alkoxy, (un)substituted alkylphenyl, etc.], useful for inhibiting resistant neoplasms where the resistance is conferred in part or in total by MRP1, were prepd. Thus, reacting 9-chloro-3-methyl-5-(piperidin-3-yl)-5H-isoxazolo[4,3-c]quinolin-4-one hydroiodide (prepn. given) with 3-pyridinepropionic acid afforded 45% I [A = N; B = CH2; R1 = 3-(3-pyridinyl)propionyl; R2 = H]. Representative compds. I demonstrated a significant effect in reversing the MRP1 multiple **drug** resistance (no data given).

IT **471895-13-3P 471895-15-5P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of piperidinyl-substituted isoxazolo[4,3-c]quinolinones for inhibiting MRP1)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 6 OF 33 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:696005 HCAPLUS
DOCUMENT NUMBER: 137:232914
TITLE: Template-fixed peptidomimetics with antimicrobial activity
INVENTOR(S): Obrecht, Daniel; Robinson, John Anthony; Vrijbloed, Jan Wim
PATENT ASSIGNEE(S): Polyphor Ltd., Switz.; Universitaet Zuerich
SOURCE: PCT Int. Appl., 262 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002070547	A1	20020912	WO 2002-EP1711	20020218

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,

UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: WO 2001-EP2072 W 20010223
OTHER SOURCE(S): MARPAT 137:232914
AB Template-fixed .beta.-hairpin peptidomimetics having sequences of the type -N-Z-CO-, where Z is a chain of 8 to 16 .alpha.-amino acid residues, and their salts inhibit the growth or kill microorganisms and cancer cells. They can be used as disinfectants for foodstuffs, cosmetics, **medicaments** or other nutrient-contg. materials or as **medicaments** to treat or prevent infections or diseases related to such infections and/or cancer. These .beta.-hairpin peptidomimetics can be manufd. by a process which is based on a mixed solid- and soln. phase synthetic strategy. Thus, a peptide having the sequence Arg-Leu-Tyr-Arg-D-Pro-Pro-Arg-Tyr-Tyr-Arg-Arg, in which the template is D-Pro-Pro, was synthesized by the solid-phase method and assayed for antimicrobial activity (MIC = 25 .mu.g/mL at a concn. of 100 .mu.g/mL in the case of Escherichia coli).
IT **274676-10-7P 458546-83-3P 458546-84-4P 458546-89-9P 458546-90-2P 458546-91-3P 458546-92-4P 458546-93-5P 458546-94-6P 458546-95-7P 458546-96-8P 458546-97-9P 458546-98-0P 458546-99-1P 458547-00-7P 458547-01-8P 458547-02-9P 458547-03-0P 458547-04-1P 458547-05-2P 458547-06-3P 458547-07-4P 458547-08-5P 458547-09-6P 458547-10-9P 458547-11-0P 458547-12-1P 458547-13-2P 458547-14-3P 458547-15-4P 458547-16-5P 458547-17-6P 458547-18-7P 458547-19-8P 458547-20-1P 458547-21-2P 458547-22-3P 458547-23-4P 458547-24-5P 458547-25-6P 458547-26-7P 458547-28-9P 458547-30-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(template-fixed peptidomimetics with antimicrobial activity)
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

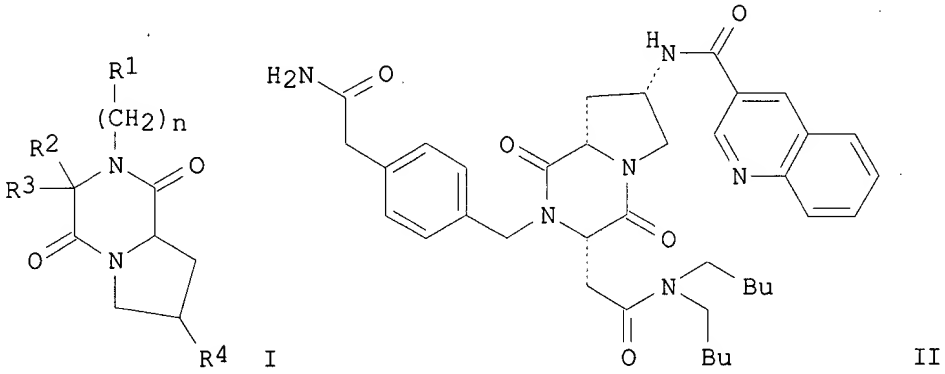
L18 ANSWER 7 OF 33 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:615615 HCAPLUS
DOCUMENT NUMBER: 137:169547
TITLE: Preparation of 1,4-dioxooctahydropyrrolo[1,2-a]pyrazines as TNF-.alpha. inhibitors for treatment of inflammation
INVENTOR(S): Boyce, Jim P.; Howbert, Jeffry J.; Tabone, John C.
PATENT ASSIGNEE(S): Celltech R & D, Inc., USA
SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002062797	A2	20020815	WO 2001-US49576	20011228
WO 2002062797	A3	20021219		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2002187984 A1 20021212 US 2001-35594 20011228
PRIORITY APPLN. INFO.: US 2000-259359P P 20001229
OTHER SOURCE(S): MARPAT 137:169547
GI



I II

AB The title diketopiperazines I [wherein R1 = (hetero)aryl ring; R2, R3, R5, R6, and R7 = independently H, (hetero)aryl, (hetero)alkyl, carbocycle aliph. ring, or heterocycle aliph. ring; n = 1-3; R4 = OR5 or NR6R7; or NR6R7 = heterocycle aliph. ring; or optical isomers, diastereomers, enantiomers, **pharmaceutically** acceptable salts thereof in isolation or mixt.] were prepd. For example, 1,4-dioxooctahydropyrrolo[1,2-a]pyrazine amide II was prepd. in a 10-step synthesis in 5.6% overall yield involving condensation and cyclization reactions. II functioned as inhibitors of TNF-.alpha.-induced apoptosis with IC50 = 8 .mu.M, TNF-.alpha.-induced expression of BFK-B with IC50 = 30 .mu.M, and binding of IL-8 or GRO-.alpha. to CXCR1 or CXCR2 with 10-30% inhibition at 20 .mu.M. The synthesis of I, their use in inhibiting cellular events such as those involving NFK-.alpha., NFK-.beta. and in the treatment of inflammation events, a combinatorial library of diverse 1,4-dioxooctahydropyrrolo[1,2-a]pyrazines, and process for their synthesis as a library and as individual compds were reported. In particular, I are disclosed including their synthesis and use in cellular events such as activation of the transcription factor, nuclear factor, TNF-.alpha., TNF-.beta., and also apoptosis.

IT **447405-81-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; prepn. of pyrrolo[1,2-a]pyrazines as TNF-.alpha. inhibitors for treatment of inflammation)

IT **174148-03-9**
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant; prepn. of pyrrolo[1,2-a]pyrazines as TNF-.alpha. inhibitors for treatment of inflammation)

L18 ANSWER 8 OF 33 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:276427 HCAPLUS
DOCUMENT NUMBER: 136:304051
TITLE: Methods of treating multiple myeloma and myeloma-induced bone resorption using integrin

antagonists
INVENTOR(S): Mundy, Gregory R.; Yoneda, Toshiyuki
PATENT ASSIGNEE(S): Board of Regents, University of Texas System, USA
SOURCE: U.S. Pat. Appl. Publ., 61 pp., Cont.-in-part of U.S. Ser. No. 805,840.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002041874	A1	20020411	US 2001-943659	20010831
WO 2000015247	A2	20000323	WO 1999-US21170	19990913
WO 2000015247	A3	20000525		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002022028	A1	20020221	US 2001-805840	20010313
US 2002159998	A1	20021031	US 2002-86217	20020221

PRIORITY APPLN. INFO.:

US 1998-100182P	P	19980914
WO 1999-US21170	W	19990913
US 2001-805840	A2	20010313
US 2001-943659	A2	20010831

AB Antagonists of .alpha.4 integrin/.alpha.4 integrin ligand adhesion, which inhibit the biol. effects of such adhesion are described and methods for their use are detailed. Such antagonists are useful in suppressing bone destruction assocd. with multiple myeloma. The homing of multiple myeloma cells to bone marrow and their .alpha.4 integrin-dependent release of bone-resorbing factors, resulting in bone destruction in patients with multiple myeloma, is inhibited. Among the examples provided are 2 which show that monoclonal antibody PS/2 to VLA-4 strongly inhibits the growth of established myeloma cells and that anti-.alpha.4 integrin antibody enhances sensitivity of myeloma cells to melphalan.

IT **410084-86-5P**, BIO 8809
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(BIO 8809; treatment of multiple myeloma and myeloma-induced bone resorption using integrin antagonists and **chemotherapeutic** agents)

IT **410084-88-7P**, BIO 9257
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(BIO 9257; treatment of multiple myeloma and myeloma-induced bone resorption using integrin antagonists and **chemotherapeutic** agents)

IT **189215-90-5P 409325-34-4P 409325-35-5P 409325-36-6P 409325-37-7P 409325-38-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(treatment of multiple myeloma and myeloma-induced bone resorption using integrin antagonists and **chemotherapeutic** agents)

L18 ANSWER 9 OF 33 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:142701 HCAPLUS
DOCUMENT NUMBER: 136:183700

TITLE: Preparation of pyrrole factor Xa inhibitors as antithrombotic agents

INVENTOR(S): Beight, Douglas Wade; Masters, John Joseph; Sawyer, Jason Scott; Shuman, Robert Theodore; Wiley, Michael Robert; Yee, Ying Kwong

PATENT ASSIGNEE(S): Eli Lilly and Company, USA

SOURCE: PCT Int. Appl., 71 pp.
CODEN: PIXXD2

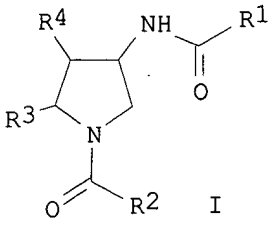
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002014308	A1	20020221	WO 2001-US21130	20010806
W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DM, DZ, EC, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001082871	A5	20020225	AU 2001-82871	20010806

PRIORITY APPLN. INFO.: US 2000-225926P P 20000817
WO 2001-US21130 W 20010806

OTHER SOURCE(S): MARPAT 136:183700

GI



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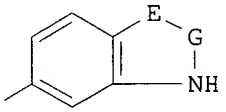

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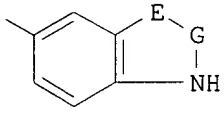


III

AB This application relates to I (e.g. 3-[(6-indolyl)carbonyl]amino-1-[[1-(4-pyridinyl)piperidin-4-yl]carbonyl]pyrrolidine hydrochloride (1); or a **prodrug** thereof or a **pharmaceutically** acceptable salt of the compd. or **prodrug** thereof) as defined herein, **pharmaceutical** compns. thereof, and its use as an inhibitor of factor Xa (some binding consts. included), as well as a process for its prepn. and intermediates therefor. In I, one of R1 and R2 is Q1; the other of R1 and R2 is Q2; wherein Q1 is 2-pyridinyl (which may bear a Me, methoxy, methylthio, fluoro or chloro substituent at the 5-position) or 3-pyridinyl (which may bear a Me, fluoro or chloro substituent at the 6-position); or Q1 is Ph which may bear 1-3 substituents at the 3-, 4- or 5-position(s) independently selected from halo, cyano, carbamoyl, aminomethyl, Me, methoxy, difluoromethoxy, hydroxymethyl, formyl, vinyl, dimethylamino, amino, hydroxy and 3,4-methylenedioxy, and in addn., the Ph may bear a 2-chloro or 2-fluoro substituent; or Q1 II or III wherein -E-G-NH- is -CH2-CH2-NH-, -C(Ra):CH-NH-, -C(Ra):N-NH-, -N:CH-NH- or -N:N-NH- in which Ra is H, fluoro, chloro, bromo or Me; Q2 is N-Rm-4-piperidinyl, N-Rm-4-piperidinyloxy, N-Rm-4-piperidinylmethoxy, in which Rm is (1-4C)alkyl, cyclohexyl, 4-tetrahydropyranyl, Ph, 4-pyridyl or

2-pyrimidinyl. When R2 is Q1, then R3 is H, COOH, N-(methyl)benzenesulfonylamino or Ph (which may be substituted at the 3-or 4-position with Me, chloro or fluoro) and R4 is H; and when R2 is Q2, then R3 is H and R4 is H, COOH, Me, N-(methyl)benzenesulfonylamino, unsubstituted Ph or Ph (which may be substituted at the 3- or 4-position with Me, chloro or fluoro). Seven example prepns. are included. For example, 1 was prepd. in 4 steps. Intermediate 1-Cbz-3-(tert-butyloxycarbonyl)aminopyrrolidine (2) was prepd. with 83% yield by adding NEt3 (26.8 mmol) to a soln. of 3-(tert-butyloxycarbonyl)aminopyrrolidine (26.8 mmol) in THF (40 mL), followed by the addn. of benzyl chloroformate (26.8 mmol) slowly. Intermediate 1-Cbz-3-[(6-indolyl)carbonyl]aminopyrrolidine (3) was prepd. with 53% yield by placing 2 (9.8 mmol) in a flask contg. HO2CCF3 (30 mL) and anisole (3.0 mL), and stirred at 0.degree. for 20 min. Workup gave the amine TFA salt, which was dissolved in DMF (20 mL) and stirred at room temp. To the soln. was added indole-6-carboxylic acid (2.72 mmol), HOBt (2.72 mmol), and DCC (2.72 mmol). Intermediate 1-Cbz-3-[[1-(tert-butyloxycarbonyl)indol-6-yl]carbonyl]aminopyrrolidine (4) was prepd. in 99% yield by dissolving 3 (2.72 mmol) in CH3CN (20 mL) and CH2Cl2 (5 mL). To the soln. was added 4-dimethylaminopyridine (2.72 mmol), diisopropylethylamine (2.72 mmol), and di-tert-Bu dicarbonate (2.86 mmol). 4 (2.69 Mmol), dissolved in EtOH (100 mL) and 1 N HCl (2.69 mmol), was hydrogenated in the presence of 5% Pd/C catalyst (0.30 g) at ambient temp. and pressure to give 3-[[1-(tert-butyloxycarbonyl)indol-6-yl]carbonylamino]pyrrolidine hydrochloride salt (0.93 g). In a sep. flask [1-(4-pyridinyl)piperidin-4-yl]carboxylic acid (3.69 mmol) was suspended in CH2Cl2 (30 mL), and thionyl chloride (5.53 mmol) was added. The reaction was refluxed for 2 h, and the solvent was removed in vacuo. The residue was dissolved in CH2Cl2 (25 mL) and added to a soln. contg. the above hydrochloride salt (0.93 g), diisopropylethylamine (2.46 mmol), and pyridine (3 mL). After workup, 1 was obtained in 56% yield.

IT **400653-48-7P**, (2S,4S)-4-[[(9-Fluorenyl)methoxy]carbonyl]amino-1-[[1-(tert-butyloxycarbonyl)indol-6-yl]carbonyl]pyrrolidine-2-carboxylic Acid **400653-50-1P**, (2S,4S)-4-(Fmoc-amino)pyrrolidine-2-carboxylic acid triflate
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; prepn. of pyrrole factor Xa inhibitors as antithrombotic agents)

IT **400653-47-6P**, (2S,4S)-4-[[1-(4-Pyridinyl)piperidin-4-yl]carbonyl]amino-1-[(6-indolyl)carbonyl]pyrrolidine-2-carboxylic Acid
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of pyrrole factor Xa inhibitors as antithrombotic agents)

IT **174148-03-9**, (2S,4S)-4-(Fmoc-amino)-1-Boc-pyrrolidine-2-carboxylic acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(reactant; prepn. of pyrrole factor Xa inhibitors as antithrombotic agents)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 10 OF 33 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:142666 HCAPLUS
DOCUMENT NUMBER: 136:200479
TITLE: Preparation of proline derivatives as dipeptidyl peptidase IV (DPP-IV) inhibitors and use thereof as **drugs**
INVENTOR(S): Kitajima, Hiroshi; Sakashita, Hiroshi; Akahoshi, Fumihiko; Hayashi, Yoshiharu
PATENT ASSIGNEE(S): Welfide Corporation, Japan
SOURCE: PCT Int. Appl., 340 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002014271	A1	20020221	WO 2001-JP6906	20010810

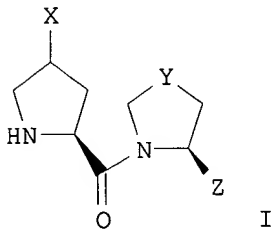
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2001077754	A5	20020225	AU 2001-77754	20010810

PRIORITY APPLN. INFO.:
JP 2000-243217 A 20000810
JP 2000-400296 A 20001228
WO 2001-JP6906 W 20010810

OTHER SOURCE(S): MARPAT 136:200479
GI



I

AB The title compds. [I; X = NR1R2, NR3COR4, NR5COR4, NR5CH2CH2NR6R7, NR8SO2R9, OR10, O2CR11; wherein R1, R2 = H, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, or they are linked to each other to form a heterocyclyl contg. 1 or 2 N atoms or O which may be a spiro ring and is optionally fused to an (un)substituted arom. ring; R3, R4 = H, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, arylalkenyl, heteroaryl, heteroarylalkyl; R5, R6, R7 = H, alkyl, acyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl, or which is optionally fused to an (un)substituted arom. ring; R8, R9, R10, R11 = H, alkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl] or **pharmacol**. acceptable salts thereof are prepd. These compds. are useful for the treatment of DPP-IV related diseases such as diabetes, obesity, HIV infection, cancer metastasis, skin diseases, prostatic hypertrophy (prostatomegaly), pericementitis, or autoimmune diseases. Thus, a soln. of 0.924 g (S)-1-[(2S,4S)-4-amino-1-tert-butoxycarbonyl-2-pyrrolidinylcarbonyl]-2-cyanopyrrolidine (prepn. given), 1.7 mL diisopropylethylamine, and 0.78 g 2-chloro-4-fluorobenzonitrile in 10 mL N-methyl-2-pyrrolidone were stirred at 80.degree. for 4 h to give 0.94 g (S)-1-[(2S,4S)-1-tert-butoxycarbonyl-4-(3-chloro-4-cyanophenyl)amino-2-pyrrolidinylcarbonyl]-2-cyanopyrrolidine which (0.93 g) was treated with HCl/EtOAc at room temp. for 15 h to give (S)-1-[(2S,4S)-4-(3-chloro-4-cyanophenyl)amino-2-pyrrolidinylcarbonyl]-2-cyanopyrrolidine hydrochloride (II). II showed IC50 of 0.13 and 0.15 nM against human blood plasma

DPP-IV and rat blood plasma DPP-IV, resp.

IT **401561-24-8P 401561-25-9P 401561-26-0P**
401561-27-1P 401561-28-2P 401561-30-6P
401561-32-8P 401561-33-9P 401561-35-1P
401562-01-4P 401562-02-5P 401562-03-6P
401562-04-7P 401562-05-8P 401562-06-9P
401562-07-0P 401562-08-1P 401562-14-9P
401562-15-0P 401564-15-6P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of proline derivs. as dipeptidyl peptidase IV (DPP-IV) inhibitors for treating DPP-IV related diseases)

IT **401564-27-0P 401564-28-1P 401564-29-2P**
401564-82-7P 401564-83-8P 401564-84-9P
401564-85-0P 401564-86-1P 401564-87-2P
401564-88-3P 401564-89-4P 401564-90-7P
401565-49-9P 401565-50-2P 401565-51-3P
401565-52-4P 401565-53-5P 401565-54-6P
401565-55-7P 401565-58-0P 401565-59-1P
401568-03-4P 401568-94-3P 401569-02-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of proline derivs. as dipeptidyl peptidase IV (DPP-IV) inhibitors for treating DPP-IV related diseases)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 11 OF 33 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:107349 HCAPLUS
DOCUMENT NUMBER: 136:167397
TITLE: Azabicyclic compounds, including 1,3-diazabicyclo[2.2.1]heptan-2-one and 1,6-diazabicyclo[3.2.1]octan-7-one derivatives, preparation thereof, and use as **medicines**, in particular as antibacterial agents
INVENTOR(S): Lampilas, Maxime; Aszodi, Jozsef; Rowlands, David Alun; Fromentin, Claude
PATENT ASSIGNEE(S): Aventis Pharma S.A., Fr.
SOURCE: PCT Int. Appl., 146 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002010172	A1	20020207	WO 2001-FR2418	20010724
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
FR 2812635	A1	20020208	FR 2000-10121	20000801
FR 2812635	B1	20021011		

PRIORITY APPLN. INFO.: FR 2000-10121 A 20000801
OTHER SOURCE(S): MARPAT 136:167397
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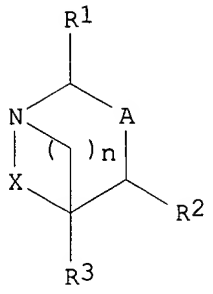

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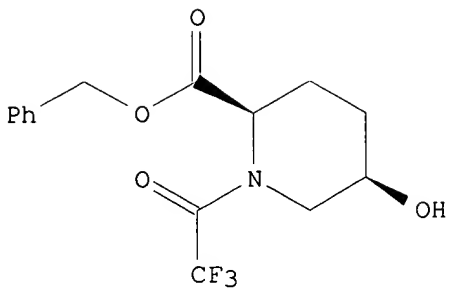

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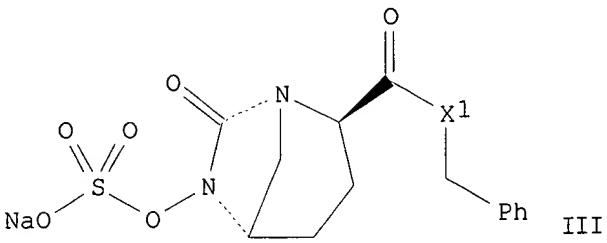


III

AB The invention concerns novel heterocyclic compds. I and their addn. salts with bases or acids [wherein: n = 1, 2; A = bond, =C(R4)-, -C(R4)=, -CH(R4)-; X = -C(O)Z- (bound at N with a C atom); Z = O, OCH2, NR8, NR8CH2, NR8O; R1 = H, CO2H, cyano, CO2R, CONR6R7, (CH2)1-2R5, C(:NR6)NHR7; R = (un)substituted alkyl, aryl, aralkyl, alkenylmethyl; R2 = H, (CH2)0-2R5; R3 = H, alkyl; R4 = H, (CH2)0-2R5; R5 = CO2H or derivs., cyano, OH or derivs., NH2 or derivs.; R6, R7 = H, (un)substituted alkyl, aryl, aralkyl, pyridylalkyl; R8 = H, OH or derivs., R, CO2H or derivs., numerous others; R1, R2, R3 are not H simultaneously]. The invention also concerns a method for prepg. I, and their use as **medicines**, in particular as antibacterial agents. I have very good activity against gram-pos. bacteria such as staphylococci, and have notable activity against gram-neg. bacteria, particularly coliform bacteria. Over 50 synthetic examples are given. For instance, the cis-isomeric hydroxy ester II (prepn. given) was converted to the triflate and treated with O-allylhydroxylamine to give a trans-isomeric propenyloxyamine deriv., which was de-N-trifluoroacetylated, cyclized with triphosgene, deallylated, sulfonated with SO3-pyridine, and ion-exchanged, to give a preferred title compd., III [X1 = O]. Another preferred compd., III [X1 = NH], had MIC values of 5 .mu.g/mL against 2 strains of S. aureus (SG511 and Exp 54146).

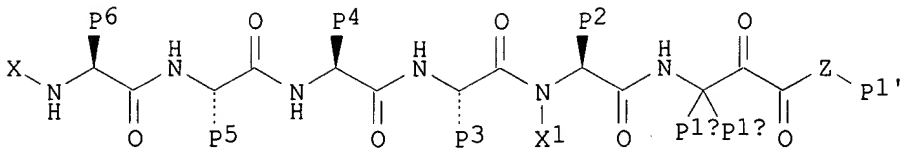
IT **396729-85-4P**, trans-1-(1,1-Dimethylethyl) 2-methyl 4-(benzoylamino)-1,2-pyrrolidinedicarboxylate **396729-86-5P**, trans-Methyl 4-(benzoylamino)-2-pyrrolidinecarboxylate hydrochloride **396729-87-6P**, trans-Methyl 4-(benzoylamino)-1-(chlorocarbonyl)-2-pyrrolidinecarboxylate hydrochloride **396730-90-8P**, trans-1-(1,1-Dimethylethyl) 2-[(4-nitrophenyl)methyl] 5-(benzoylamino)-1,2-piperidinedicarboxylate **396730-91-9P**, trans-(4-Nitrophenyl)methyl 5-(benzoylamino)-2-piperidinecarboxylate hydrochloride **396730-92-0P**, trans-(4-Nitrophenyl)methyl 5-(benzoylamino)-1-(chlorocarbonyl)-2-piperidinecarboxylate **396730-99-7P**, trans-1-(1,1-Dimethylethyl) 2-[(4-nitrophenyl)methyl] 5-(acetylamino)-1,2-piperidinedicarboxylate **396731-01-4P**, trans-1-(1,1-Dimethylethyl) 2-[(4-nitrophenyl)methyl] 5-[[(2-propenyloxy)carbonyl]amino]-1,2-piperidinedicarboxylate

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; prepn. of azabicyclic compds. as antibacterial agents)
IT **396731-03-6**, trans-Phenylmethyl 5-(benzoylamino)-1-(chlorocarbonyl)-2-piperidinecarboxylate
RL: RCT (Reactant); RACT (Reactant or reagent)
(precursor; prepn. of azabicyclic compds. as antibacterial agents)
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 12 OF 33 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:90074 HCAPLUS
DOCUMENT NUMBER: 136:151440
TITLE: Preparation of novel peptides as NS3-serine protease inhibitors of hepatitis C virus
INVENTOR(S): Saksena, Anil K.; Girijavallabhan, Viyyoor Moopil; Lovey, Raymond G.; Jao, Edwin E.; Bennett, Frank; McCormick, Jinping; Wang, Haiyan; Pike, Russell E.; Bogen, Stephane L.; Liu, Yi-Tsung; Arasappan, Ashok; Parekh, Tejal; Pinto, Patrick A.; Njoroge, F. George; Ganguly, Ashit K.; Brunck, Terence K.; Kemp, Scott Jeffrey; Levy, Odile Esther; Lim-Wilby, Marguerita
PATENT ASSIGNEE(S): Schering Corporation, USA; Corvas International, Inc.
SOURCE: PCT Int. Appl., 197 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002008256	A2	20020131	WO 2001-US22826	20010719
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003036501	A1	20030220	US 2001-909062	20010719
EP 1301528	A2	20030416	EP 2001-959046	20010719
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: US 2000-220109P P 20000721
WO 2001-US22826 W 20010719
OTHER SOURCE(S): MARPAT 136:151440
GI



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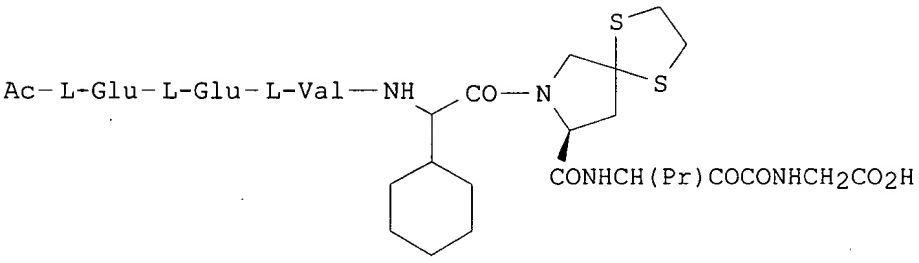


II

AB Novel peptides I [Z = O, NH or substituted imino; X = (un)substituted alkylsulfonyl, heterocyclylsulfonyl, heterocyclylalkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylcarbonyl, heterocyclylcarbonyl, heterocyclylalkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, heterocyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkyaminocarbonyl, heterocyclylaminocarbonyl, arylaminocarbonyl, or heteroarylaminocarbonyl; X1 = H, alkyl, arylmethyl; P1a, P1b, P2-P6 = H, (un)substituted alkyl, alkenyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl; P1a and P1b may optionally be joined to each other to form a spirocyclic or spiroheterocyclic ring contg. 0-6 oxygen, nitrogen, sulfur, or phosphorus atoms; P1' = H, (un)substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl] having HCV protease inhibitory activity are disclosed. Thus, peptide II was prepd. via peptide coupling in soln. and showed Ki = 1-100 nM for inhibition of HCV protease.

IT **393520-33-7P 393520-74-6P 393520-79-1P 393522-68-4P 393522-74-2P 393522-76-4P 393522-79-7P 393522-81-1P 393522-93-5P 393522-96-8P 393522-99-1P 393523-06-3P 393523-09-6P**

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of novel peptides as NS3-serine protease inhibitors of hepatitis C virus)

IT **176486-63-8P 189215-90-5P 393524-17-9P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(prepn. of novel peptides as NS3-serine protease inhibitors of hepatitis C virus)

L18 ANSWER 13 OF 33 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:90062 HCAPLUS
DOCUMENT NUMBER: 136:167698
TITLE: Preparation of peptides as NS3-serine protease inhibitors of hepatitis C virus
INVENTOR(S): Saksena, Anil K.; Girijavallabhan, Viyyoor Moopil; Lovey, Raymond G.; Jao, Edwin E.; Bennett, Frank;

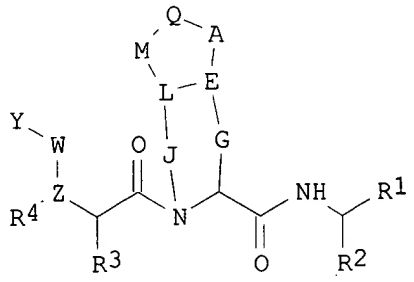
McCormick, Jinping L.; Wang, Haiyan; Pike, Russell E.; Bogen, Stephane L.; Chan, Tin-Yau; Liu, Yi-Tsung; Zhu, Zhaoning; Njoroge, F. George; Arasappan, Ashok; Parekh, Tejal N.; Ganguly, Ashit K.; Chen, Kevin X.; Venkatraman, Srikanth; Vaccaro, Henry A.; Pinto, Patrick A.; Santhanam, Bama; Wu, Wanli; Hendrata, Siska; Huang, Yuhua; Kemp, Scott Jeffrey; Levy, Odile Esther; Lim-Wilby, Marguerita; Tamura, Susan Y.
PATENT ASSIGNEE(S): Schering Corporation, USA; Corvas International, Inc.
SOURCE: PCT Int. Appl., 536 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002008244	A2	20020131	WO 2001-US22678	20010719
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001076988	A5	20020205	AU 2001-76988	20010719

PRIORITY APPLN. INFO.: US 2000-220108P P 20000721
WO 2001-US22678 W 20010719

OTHER SOURCE(S): MARPAT 136:167698
GI



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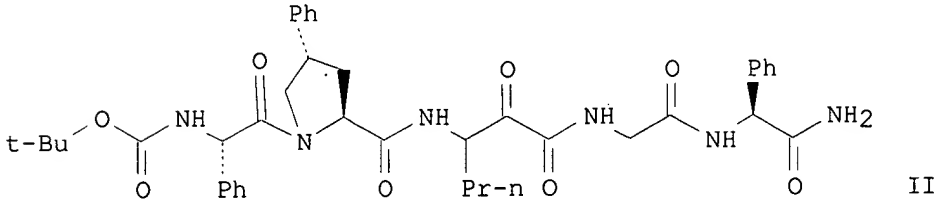


II

AB Peptides I were prepd. wherein Y is alkyl, alkyl-aryl, heteroaryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkylheteroaryl, cycloalkyl, alkyloxy, alkylaryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, cycloalkyloxy,, alkylamino, arylamino, alkylarylamino, arylamino, heteroarylamino, cycloalkylamino and heterocycloalkylamino; R1 is acyl,

borate; Z is selected from O, N, CH or CR; W, Q, G, J, L, M independently maybe present or absent; W is C=O, C=S, C(=N-CN), or SO; Q is CH, N, P, alkylidene, O, amine,S, or SO; A is O, CH, alkylidene, amine, S, SO or bond; E is CH, N, alkylidene, or double bond; G is alkylidene; J is alkylidene, SO, NH, NR, O; L is CH, alkylidene, O, S or NR; M is O, NR,S, SO, alkylidene; p is 0 to 6; and R-R4 are independently selected from the group consisting of H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, halogen; (cycloalkyl)alkyl and (heterocycloalkyl)alkyl, which have HCV protease inhibitory activity as well as methods for prepg. such compds. In another embodiment, the invention discloses **pharmaceutical** compns. comprising such compds. as well as methods of using them to treat disorders assocd. with the HCV protease. Thus peptide II was prepd. and tested as antiviral agent and NS3-serine protease inhibitors of hepatitis C virus with Ki ranges in category A = 1-100 nM; category B = 101-1,000 nM; category C > 1000 nM. Also disclosed is the use of I for the manuf. of a **medicament** for treating HCV, AIDS, and related disorders.

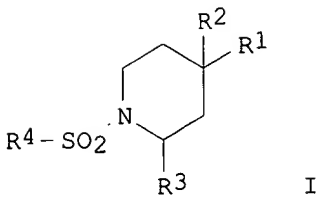
IT **394722-90-8P 394722-93-1P 394722-97-5P**
394723-02-5P 394723-07-0P 394723-08-1P
394723-09-2P 394723-14-9P 394723-16-1P
394723-17-2P 394723-18-3P 394730-81-5P
394730-82-6P
RL: IMF (Industrial manufacture); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of peptides as NS3-serine protease inhibitors of hepatitis C virus)

IT **394735-12-7DP**, polymer support
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of peptides as NS3-serine protease inhibitors of hepatitis C virus)

L18 ANSWER 14 OF 33 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:842299 HCAPLUS
DOCUMENT NUMBER: 135:371642
TITLE: Preparation of pipecolic acids and matrix metalloproteinase inhibitors
INVENTOR(S): Noda, Atsushi; Kobayashi, Yoshinori; Toyama, Takeshi
PATENT ASSIGNEE(S): Kotobuki Seiyaku Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 27 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2001322977	A2	20011120	JP 2000-140145	20000512
US 2001056184	A1	20011227	US 2001-852704	20010511
GB 2364703	A1	20020206	GB 2001-11594	20010511
DE 10123349	A1	20011129	DE 2001-10123349	20010514

PRIORITY APPLN. INFO.: JP 2000-140145 A 20000512
OTHER SOURCE(S): MARPAT 135:371642
GI



I

AB Title compds. I [R1R2 = :O, :NOR9; R9 = H, lower alkyl, benzyl; R1 = H; R2 = R5R6; R5 = O, NH, NHCO, NHSO2; R6 = H, lower alkyl, indolyl, N-oxidopyridyl, etc.; R3 = CO2H, CO2Et, CO2Me, CH2N(OH)CHO, CONHOH; R4 = lower alkyl, thienyl, C6H4R8; R8 = OH, lower alkyl, alkoxy, NO2, halo, etc.] or their **pharmaceutically** acceptable salts are prepd. (2R,4R)-4-amino-2-methoxycarbonyl-1-[4-(4-methoxyphenyl)benzene sulfonyl]piperidine (500 mg) was reacted with isocaproic acid in the presence of WSCDI and N-methylmorpholine in DMF-CH2Cl2 overnight to give 500 mg (2R,4R)-4-(4-methylpentanoyl)amino-2-methoxycarbonyl-1-[4-(4-methoxyphenyl)benzenesulfonyl]-piperidine, which was treated with LiOH in THF-H2O overnight to give (2R,4R)-2-carboxy-4-(4-methylpentanoyl)amino-1-[4-(4-methoxyphenyl)benzenesulfonyl]piperidine showing good inhibitory activity against MMP-1 in vitro.

IT **374536-69-3P 374536-71-7P**, (2R,4R)-2-Carboxy-4-(4-methylpentanoylamino)-1-(2-thiophenesulfonyl)piperidine **374536-84-2P**, (2R,4R)-4-Acetylamino-2-carboxy-1-(4-methoxybenzenesulfonyl)piperidine **374536-91-1P**, (2R,4R)-4-Acetylamino-2-carboxy-1-[(4-(4-chlorophenyl)benzene)sulfonyl]piperidine **374537-04-9P**, (2R,4S)-4-Acetylamino-2-carboxy-1-[(4-(4-methoxyphenyl)benzene)sulfonyl]piperidine **374537-28-7P**, (2R,4R)-2-Carboxy-1-(4-methoxybenzenesulfonyl)-4-(((pyridyl-2-yl)carbonyl)amino)piperidine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of pipecolic acids for matrix metalloproteinase inhibitors)

IT **374536-65-9P**, (2R,4R)-2-Carboxy-1-(4-methoxybenzenesulfonyl)-4-(4-methylpentanoylamino)piperidine **374536-66-0P** **374536-67-1P**, (2R,4R)-2-Carboxy-1-(4-methoxybenzenesulfonyl)-4-(4-methoxybenzoylamino)piperidine **374536-68-2P 374536-70-6P**, (2R,4R)-2-Carboxy-4-(4-methoxybenzoylamino)-1-(2-thiophenesulfonyl)piperidine **374536-72-8P**, (2R,4R)-1-(4-Bromobenzenesulfonyl)-2-carboxy-4-(4-methylpentanoylamino)piperidine **374536-73-9P**, (2R,4R)-1-(4-Bromobenzenesulfonyl)-2-carboxy-4-(4-methoxybenzoylamino)piperidine **374536-74-0P 374536-77-3P** **374536-78-4P 374536-81-9P**, (2R,4R)-2-Carboxy-1-(4-hydroxybenzenesulfonyl)-4-(4-methylpentanoylamino)piperidine **374536-82-0P 374536-83-1P**, (2R,4R)-4-Acetylamino-2-carboxy-1-[(4-(4-hydroxyphenyl)benzene)sulfonyl]piperidine **374536-90-0P**, (2R,4R)-2-Carboxy-1-[(4-(4-chlorophenyl)benzene)sulfonyl]-4-(4-methylpentanoylamino)piperidine **374536-92-2P**, (2R,4R)-2-Carboxy-1-[(4-(4-methoxyphenyl)benzene)sulfonyl]-4-(2-thiophenecarbonylamino)piperidine **374536-93-3P**, (2R,4R)-2-Carboxy-1-[(4-(4-methoxyphenyl)benzene)sulfonyl]-4-(2-pyridinecarbonylamino)piperidine **374536-94-4P**, (2R,4R)-2-Carboxy-1-[(4-(4-chlorophenyl)benzene)sulfonyl]-4-(2-pyridinecarbonylamino)piperidine **374536-95-5P**, (2R,4R)-2-Carboxy-1-[(4-(4-methoxyphenyl)benzene)sulfonyl]-4-(4-nitrobenzoylamino)piperidine **374536-96-6P 374536-97-7P**, (2R,4R)-2-Carboxy-4-(4-methylpentanoylamino)-1-(4-nitrobenzenesulfonyl)piperidine

374536-98-8P, (2R,4R)-2-Carboxy-4-(4-methylpentanoylamino)-1-[(4-(4-nitrophenyl)benzene)sulfonyl]piperidine **374537-00-5P**, (2S,4S)-2-Carboxy-1-(4-methoxybenzenesulfonyl)-4-[(5-(4-methoxyphenoxy)pentanoyl)amino]piperidine **374537-01-6P**, (2S,4S)-2-Carboxy-1-(4-methoxybenzenesulfonyl)-4-(4-methylpentanoylamino)piperidine **374537-02-7P**, (2S,4S)-2-Carboxy-1-(4-methoxybenzenesulfonyl)-4-(4-methoxybenzoylamino)piperidine **374537-03-8P**, (2S,4S)-4-Acetylamino-2-carboxy-1-(4-methoxybenzenesulfonyl)piperidine **374537-05-0P**, (2R,4R)-2-Hydroxyaminocarbonyl-1-(4-methoxybenzenesulfonyl)-4-(4-methylpentanoylamino)piperidine **374537-06-1P**, (2R,4R)-2-Hydroxyaminocarbonyl-1-(4-methoxybenzenesulfonyl)-4-[(5-(4-methoxyphenoxy)pentanoyl)amino]piperidine **374537-07-2P**, (2R,4R)-2-Hydroxyaminocarbonyl-1-(4-methoxybenzenesulfonyl)-4-(4-methoxybenzoylamino)piperidine **374537-08-3P 374537-09-4P 374537-10-7P**, (2R,4R)-2-Hydroxyaminocarbonyl-4-(4-methoxybenzoylamino)-1-(2-thiophenesulfonyl)piperidine **374537-11-8P**, (2R,4R)-2-Hydroxyaminocarbonyl-4-(4-methylpentanoylamino)-1-(2-thiophenesulfonyl)piperidine **374537-12-9P**, (2R,4R)-2-Hydroxyaminocarbonyl-1-[(3-(4-methoxyphenyl)benzene)sulfonyl]-4-(4-methylpentanoylamino)piperidine **374537-13-0P**, (2R,4R)-2-Hydroxyaminocarbonyl-1-[(3-(4-hydroxyphenyl)benzene)sulfonyl]-4-(4-methylpentanoylamino)piperidine **374537-14-1P**, (2R,4R)-2-Hydroxyaminocarbonyl-1-[(2-(4-methoxyphenyl)benzene)sulfonyl]-4-(4-methylpentanoylamino)piperidine **374537-15-2P**, (2R,4R)-2-Hydroxyaminocarbonyl-1-[(2-(4-hydroxyphenyl)benzene)sulfonyl]-4-(4-methylpentanoylamino)piperidine **374537-17-4P 374537-18-5P 374537-19-6P**, (2R,4R)-4-Benzoylamino-2-hydroxyaminocarbonyl-1-[(4-(4-methoxyphenyl)benzene)sulfonyl]piperidine **374537-20-9P 374537-23-2P**, (2R,4R)-2-Hydroxyaminocarbonyl-1-(4-hydroxybenzenesulfonyl)-4-(4-methylpentanoylamino)piperidine **374537-24-3P**, (2R,4R)-4-Acetylamino-2-hydroxyaminocarbonyl-1-[(4-(4-methoxyphenyl)benzene)sulfonyl]piperidine **374537-25-4P**, (2R,4R)-4-Acetylamino-2-hydroxyaminocarbonyl-1-[(4-(4-hydroxyphenyl)benzene)sulfonyl]piperidine **374537-26-5P**, (2R,4R)-4-Acetylamino-2-hydroxyaminocarbonyl-1-(4-methoxybenzenesulfonyl)piperidine **374537-27-6P**, (2R,4R)-2-Hydroxyaminocarbonyl-4-(4-methylpentanoylamino)-1-[(4-(4-nitrophenyl)benzene)sulfonyl]piperidine **374537-29-8P**, (2R,4R)-2-Hydroxyaminocarbonyl-1-(4-methoxybenzenesulfonyl)-4-(((pyridyl-2-yl)carbonyl)amino)piperidine **374537-31-2P**, (2R,4R)-1-[(4-(4-Chlorophenyl)benzene)sulfonyl]-2-hydroxyaminocarbonyl-4-(4-methylpentanoylamino)piperidine **374537-32-3P**, (2R,4R)-4-Acetylamino-1-[(4-(4-chlorophenyl)benzene)sulfonyl]-2-hydroxyaminocarbonylpiperidine **374537-33-4P**, (2R,4R)-2-Hydroxyaminocarbonyl-1-[(4-(4-methoxyphenyl)benzene)sulfonyl]-4-(2-pyridinecarbonylamino)piperidine **374537-34-5P**, (2R,4R)-1-[(4-(4-Chlorophenyl)benzene)sulfonyl]-2-hydroxyaminocarbonyl-4-(2-pyridinecarbonylamino)piperidine **374537-35-6P**, (2R,4R)-2-Hydroxyaminocarbonyl-1-[(4-(4-methoxyphenyl)benzene)sulfonyl]-4-(4-nitrobenzoylamino)piperidine **374537-36-7P**, (2R,4R)-2-Hydroxyaminocarbonyl-4-(3-indolecarbonylamino)-1-((4-(4-methoxyphenyl)benzene)sulfonyl)piperidine **374537-37-8P**, (2R,4R)-2-Hydroxyaminocarbonyl-4-(4-methylpentanoylamino)-1-(4-nitrobenzenesulfonyl)piperidine **374537-38-9P**, (2S,4S)-2-Hydroxyaminocarbonyl-1-(4-methoxybenzenesulfonyl)-4-[(5-(4-methoxyphenoxy)pentanoyl)amino]piperidine **374537-39-0P**, (2S,4S)-2-Hydroxyaminocarbonyl-1-(4-methoxybenzenesulfonyl)-4-(4-methylpentanoylamino)piperidine **374537-40-3P**, (2S,4S)-2-Hydroxyaminocarbonyl-1-(4-methoxybenzenesulfonyl)-4-(4-methoxybenzoylamino)piperidine **374537-41-4P**,

(2S,4S)-4-Acetylamino-2-hydroxyaminocarbonyl-1-(4-methoxybenzenesulfonyl)piperidine **374537-42-5P**, (2R,4S)-4-Acetylamino-2-hydroxyaminocarbonyl-1-[(4-(4-methoxyphenyl)benzene)sulfonyl]piperidine **374537-45-8P** **374537-46-9P** **374537-47-0P** **374537-48-1P** **374537-49-2P** **374538-07-5P**, (2R,4R)-2-Carboxy-1-[(2-(4-hydroxyphenyl)benzene)sulfonyl]-4-(4-methylpentanoylamino)piperidine **374538-08-6P**, (2R,4R)-2-Carboxy-1-[(3-(4-methoxyphenyl)benzene)sulfonyl]-4-(4-methylpentanoylamino)piperidine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of pipecolic acids for matrix metalloproteinase inhibitors)

IT **374537-60-7**, (2R,4S)-2-Methoxycarbonyl-4-(4-methylpentanoylamino)piperidine
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of pipecolic acids for matrix metalloproteinase inhibitors)

IT **374537-54-9P** **374537-55-0P** **374537-57-2P** **374537-59-4P** **374537-61-8P** **374537-66-3P** **374537-67-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of pipecolic acids for matrix metalloproteinase inhibitors)

L18 ANSWER 15 OF 33 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:816697 HCAPLUS
DOCUMENT NUMBER: 135:339205
TITLE: STAT4 and STAT6 binding dipeptide derivatives
INVENTOR(S): Mckinney, Judi; Raimundo, Brian C.; Cushing, Timothy D.; Yoshimura, Hiromitsu; Ohuchi, Yutaka; Hiratate, Akira; Fukushima, Hiroshi; Xu, Feng; Peto, Csaba
PATENT ASSIGNEE(S): Tularik Inc., USA; Taisho Pharmaceutical Co., Ltd.
SOURCE: PCT Int. Appl., 85 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001083517	A1	20011108	WO 2000-US12079	20000503

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: WO 2000-US12079 20000503
OTHER SOURCE(S): MARPAT 135:339205
AB Compds. and compns. are provided along with methods for their use as immunomodulators.
IT **371919-32-3P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(STAT4 and STAT6 binding dipeptide derivs. and their use as immunomodulators and treatment of STAT6-dependent diseases)
IT **371919-48-1** **371919-49-2** **371919-51-6** **371919-53-8** **371920-03-5** **371920-04-6**

371920-05-7 371920-06-8 371920-07-9
371920-08-0 371920-09-1 371920-10-4
371920-11-5 371920-12-6 371920-13-7
371920-14-8 371920-15-9 371920-16-0
371920-17-1
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(STAT4 and STAT6 binding dipeptide derivs. and their use as immunomodulators and treatment of STAT6-dependent diseases)

IT **371919-37-8P 371919-38-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(STAT4 and STAT6 binding dipeptide derivs. and their use as immunomodulators and treatment of STAT6-dependent diseases)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 16 OF 33 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:713294 HCAPLUS
DOCUMENT NUMBER: 135:257169
TITLE: Preparation of cyclic .beta.-amino acid derivatives as inhibitors of matrix metalloproteases and TNF-.alpha.
INVENTOR(S): Duan, Jingwu; Ott, Gregory; Chen, Linhua; Lu, Zhonghui; Maduskuie, Thomas P., Jr.; Voss, Matthew E.; Xue, Chu-Biao
PATENT ASSIGNEE(S): Dupont Pharmaceuticals Company, USA
SOURCE: PCT Int. Appl., 298 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001070673	A2	20010927	WO 2001-US8334	20010315
WO 2001070673	A3	20020314		
W: AT, AU, BR, CA, CH, CN, CZ, DE, DK, EE, ES, FI, HU, IN, JP, KR, LT, LU, LV, MX, NZ, PL, PT, RO, SE, SG, SI, SK, UA, VN, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
EP 1263755	A2	20021211	EP 2001-924170	20010315
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR				
US 2002016336	A1	20020207	US 2001-811233	20010316

PRIORITY APPLN. INFO.: US 2000-190182P P 20000317
US 2000-233373P P 20000918
US 2000-255539P P 20001214
WO 2001-US8334 W 20010315

OTHER SOURCE(S): MARPAT 135:257169

AB Novel cyclic .beta.-amino acid derivs. A-CRR2aCRR2bNR1CO-Z-Ua-Xa-Ya-Za [A = CO2H, CH2CO2H, SH, CH2SH, S(O)Ra:NH (Ra = H, alkyl, Ph, benzyl), P(O)(OH)2, etc.; CRCR is a substituted 3-13 membered nonarom. carbocyclic or heterocyclic ring; Z is absent or substituted C3-13 carbocycle or 5-14 membered heterocycle; Ua is absent or O, NRa1 (Ra1 = H, alkyl), CO, CO2, O2C, CONRa1, S(O)p (p = 0-2), etc.; Xa is absent or C1-10 alkylene, C2-10 alkenylene or alkynylene; Ya is absent or O, NRa1, S(O)p or CO; Za is H, substituted C3-13 carbocycle or 5-14 membered heterocycle; R1 is H, C1-4 alkyl, Ph, benzyl; R2a is H, C1-6 alkyl, ORa, NRaRa1 or S(O)pRa; R2b is H, C1-6 alkyl (with provisos)] or **pharmaceutically** acceptable salts were prepd. as metalloprotease and TNF-.alpha. inhibitors. Thus,

(3S,4S)-N-hydroxy-1-isopropyl-4-[[4-[(2-methyl-4-quinolinyl)methoxy]benzoyl]amino]-3-pyrrolidinecarboxamide was prepd. by a multistep procedure starting with condensation of benzyl Me maleate, glycine, and paraformaldehyde to form 3,4-pyrroledicarboxylate diester and involving amidation of 4-[(2-methyl-4-quinolinyl)methoxy]benzoic acid.

IT **362484-13-7P 362484-14-8P 362484-15-9P**
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RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of cyclic .beta.-amino acid derivs. as inhibitors of matrix metalloproteases and TNF-.alpha.)

IT 362487-19-2P 362487-20-5P 362487-22-7P
362487-23-8P 362487-25-0P 362487-26-1P
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362491-12-1P 362492-71-5P 362492-72-6P
362492-74-8P 362492-75-9P 362492-77-1P
362492-78-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of cyclic .beta.-amino acid derivs. as inhibitors of matrix metalloproteases and TNF-.alpha.)

IT 362489-75-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of cyclic .beta.-amino acid derivs. as inhibitors of matrix metalloproteases and TNF-.alpha.)

IT 362488-40-2P 362488-44-6P 362488-46-8P
362488-47-9P 362488-49-1P 362488-53-7P

362488-54-8P 362488-69-5P 362488-70-8P
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362489-84-7P 362489-86-9P 362489-88-1P
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362489-94-9P 362489-96-1P 362489-98-3P
362490-00-4P 362490-02-6P 362490-04-8P
362490-06-0P 362490-07-1P 362490-09-3P
362490-11-7P 362490-14-0P 362490-16-2P
362490-18-4P 362490-21-9P 362490-28-6P
362490-30-0P 362490-32-2P 362490-34-4P
362490-38-8P 362490-39-9P 362490-40-2P
362490-41-3P 362490-80-0P 362490-81-1P
362490-84-4P 362490-86-6P 362490-88-8P
362491-92-7P 362491-94-9P 362492-38-4P
362492-40-8P 362516-53-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of cyclic .beta.-amino acid derivs. as inhibitors of matrix metalloproteases and TNF-.alpha.)

L18 ANSWER 17 OF 33 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:564832 HCAPLUS
DOCUMENT NUMBER: 135:147457
TITLE: **Pharmaceutical** compositions containing anti-.beta.1-integrin compounds, their preparation, and their use in inhibiting cell adhesion
INVENTOR(S): Zheng, Zhongli; Cuervo, Julio H.; Lin, KoChung; Ateeq, Humayun Saleem
PATENT ASSIGNEE(S): Biogen, Inc., USA
SOURCE: PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001054690	A1	20010802	WO 2001-US2783	20010126
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1253923	A1	20021106	EP 2001-905160	20010126
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: US 2000-178585P P 20000128
WO 2001-US2783 W 20010126

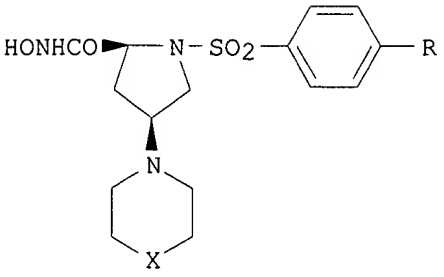
OTHER SOURCE(S): MARPAT 135:147457
AB Org. Anti-.beta.1-integrin compds. useful for inhibiting cell-adhesion are disclosed. **Pharmaceutical** compns. contg. the compds. are included, as is compd. prepn.
IT **352275-42-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(anti-.beta.1-integrin compds., **pharmaceutical** compns., prepn., and use in inhibiting cell adhesion)
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 18 OF 33 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:367621 HCAPLUS
DOCUMENT NUMBER: 135:215823
TITLE: Applications of protein epitope mimetics in vaccine design. A new supersecondary structure in the circumsporozoite protein of Plasmodium falciparum?
AUTHOR(S): Pfeiffer, Bernhard; Moreno, Rafael; Moehle, Kerstin; Zurbriggen, Rinaldo; Gluck, Reinhard; Pluschke, Gerd; Robinson, John A.
CORPORATE SOURCE: Institute of Organic Chemistry, University of Zurich, Zurich, CH-8057, Switz.
SOURCE: Chimia (2001), 55(4), 334-339
CODEN: CHIMAD; ISSN: 0009-4293
PUBLISHER: Neue Schweizerische Chemische Gesellschaft
DOCUMENT TYPE: Journal
LANGUAGE: English
AB An approach to synthetic vaccine design is illustrated, focusing on the immunodominant (NPNA)n repeat region of the circumsporozoite (CS) protein of the malaria parasite Plasmodium falciparum. Modeling suggests that the NPNAN motif may adopt a helical .beta.-turn, which is tandemly repeated in the CS protein to generate a novel supersecondary structure. Cyclic peptidomimetics of this NPNAN motif were synthesized and shown by NMR to adopt helical turns in aq. soln. When incorporated into Immunopotentiating Reconstituted Influenza Virosomes (IRIVs), humoral immune responses were generated in mice that cross-react with native CS protein on sporozoites. IRIVs are a human-compatible delivery system that appear generally suitable for inducing antibody responses against conformational epitopes using constrained peptidomimetics. This approach may offer great potential for the design of molecularly defined synthetic vaccines, including those targeted against multiple antigens and development stages of P. falciparum, or against other infectious agents.
IT **357916-36-0**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(applications of protein epitope mimetics in vaccine design. for Plasmodium falciparum)
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 19 OF 33 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:786254 HCAPLUS
DOCUMENT NUMBER: 134:101151
TITLE: Development of new hydroxamate matrix metalloproteinase inhibitors derived from functionalized 4-aminoprolines
AUTHOR(S): Natchus, Michael G.; Bookland, Roger G.; De, Biswanath; Almstead, Neil G.; Pikul, Stanislaw; Janusz, Michael J.; Heitmeyer, Sandra A.; Hookfin, Erin B.; Hsieh, Lily C.; Dowty, Martin E.; Dietsch, Charles R.; Patel, Vikram S.; Garver, Susan M.; Gu, Fei; Pokross, Matthew E.; Mieling, Glen E.; Baker, Timothy R.; Foltz, David J.; Peng, Sean X.; Bornes, David M.; Strojnowski, Michael J.; Taiwo, Yetunde O.
CORPORATE SOURCE: Procter and Gamble Pharmaceuticals, Mason, OH, 45040, USA
SOURCE: Journal of Medicinal Chemistry (2000), 43(26), 4948-4963

CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 134:101151
GI



I

AB A series of hydroxamates was prepd. from an aminoproline scaffold and tested for efficacy as matrix metalloproteinase (MMP) inhibitors. Detailed SAR for the series is reported for five enzymes within the MMP family, and a no. of inhibitors, such as compd. I (X = XH2, R = OPh), display broad-spectrum activity with sub-nanomolar potency for some enzymes. Modifications of the P1' portion of the mol. played a key role in affecting both potency and selectivity within the MMP family. Longer-chain aliph. substituents in this region of the mol. tended to increase potency for MMP-3 and decrease potency for MMP-1, as exemplified by compds. I (X = O; R = OMe, OPr, or OBu), while arom. substituents, as in compd. I (X = O, R = OPh), generated broad-spectrum inhibition. The data is rationalized based upon X-ray crystal data which is also presented. While the in vitro peroral absorption seemed to be less predictable, it tended to decrease with longer and more hydrophilic substituents. Finally, a rat model of osteoarthritis was used to evaluate the efficacy of these compds., and a direct link was established between their **pharmacokinetics** and their in vivo efficacy.

IT **317860-46-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(development of hydroxamate matrix metalloproteinase inhibitors derived from functionalized aminoprolines)

IT **204071-93-2P 204071-94-3P 317860-36-9P**
317860-38-1P 317860-40-5P 317860-42-7P
317860-44-9P 317860-48-3P 317860-49-4P
317860-51-8P 317860-53-0P 317860-55-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(development of hydroxamate matrix metalloproteinase inhibitors derived from functionalized aminoprolines)

IT **317860-96-1P 317861-00-0P 317861-01-1P**
317861-02-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(development of hydroxamate matrix metalloproteinase inhibitors derived from functionalized aminoprolines)

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 20 OF 33 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:785349 HCAPLUS
DOCUMENT NUMBER: 134:110362
TITLE: Antinociceptive activity of the novel fentanyl analogue iso-carfentanil in rats
AUTHOR(S): Vuckovic, Sonja; Prostran, Milica; Ivanovic, Milovan; Ristovic, Zorana; Stojanovic, Radan
CORPORATE SOURCE: Department of Clinical Pharmacology, Pharmacology and Toxicology, School of Medicine, University of Belgrade, Belgrade, 11129, Yugoslavia
SOURCE: Japanese Journal of Pharmacology (2000), 84(2), 188-195
CODEN: JJPAAZ; ISSN: 0021-5198
PUBLISHER: Japanese Pharmacological Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A large no. of fentanyl analogs have been synthesized so far, both to establish the structure-activity-relationship (SAR) and to find novel, clin. useful antinociceptive **drugs**. In this study, the newly synthesized fentanyl analog 3-carbomethoxy fentanyl (iso-carfentanil) was compared to fentanyl for its antinociceptive activity (tail-immersion test) in rats. It was revealed that the introduction of a 3-carbomethoxy group in the piperidine ring of fentanyl skeleton reduced the potency and shortened the duration of action of the parent compd., i.e., fentanyl. The antinociceptive potency of 3-carbomethoxy fentanyl is influenced mainly by the steric factor (voluminosity of the carbomethoxy group and the cis/trans isomerism), while the chem. nature of the group is probably irrelevant. This is in agreement with SAR studies of other 3-substituted fentanyl analogs. In contrast to potency, the duration of action is not affected by cis/trans isomerism. It is assumed that the time course of action of 3-carbomethoxy fentanyl is influenced by the nature of the carbomethoxy group. Since the potency and the duration of action of this novel antinociceptive compd. are interesting from the aspect of SAR studies and have potential promise for clin. application, 3-carbomethoxy fentanyl deserves to be extensively evaluated.

IT **203639-44-5 203639-45-6**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(antinociceptive activity of the novel fentanyl analog iso-carfentanil in rats)

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

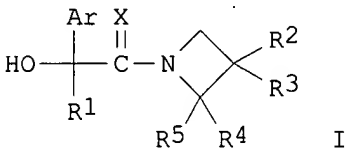
L18 ANSWER 21 OF 33 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:368356 HCAPLUS
DOCUMENT NUMBER: 133:17372
TITLE: Preparation of 1-acylazetidine derivatives as selective inhibitors of M3-muscarinic receptor
INVENTOR(S): Tsuchiya, Yoshimi; Nomoto, Takashi; Nomoto, Takashi; Kawakami, Kumiko; Ohwaki, Kenji; Nishikibe, Masaru
PATENT ASSIGNEE(S): Banyu Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 72 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000031078	A1	20000602	WO 1999-JP6497	19991119

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,

IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI,
SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: JP 1998-331040 A 19981120
OTHER SOURCE(S): MARPAT 133:17372
GI



I

AB Compds. represented by general formula [I; wherein Ar is an aryl or heteroaryl group which may optionally bear a substituent selected from the group consisting of halogeno, lower alkyl and lower alkoxy; R1 is optionally fluorinated C3-6 cycloalkyl; R2 and R4 are each hydrogen, -(A1)m-NH-B, or the like; wherein A1 is an optionally lower alkyl-substituted bivalent aliph. hydrocarbon group; m is 0 or 1; B is hydrogen or C1-6 aliph. hydrocarbon group optionally having a substituent selected from lower alkyl and aryl; R3 and R5 are each hydrogen, an aliph. C1-6 hydrocarbon group optionally substituted with lower alkyl, or the like; and X is oxygen or sulfur] are prepd. These compds. exhibit selective muscarinic M3 receptor antagonism and are excellent in peroral activities, persistency of action, and in vivo kinetics, thus being useful as treating agents for respiratory, urol. or digestive diseases which have little adverse effect and are safe and efficacious. Thus, 7-benzyl-2,7-diazaspiro[3.5]nonane was condensed with (2R)-2-((1R)-3,3-difluorocyclopentyl)-2-hydroxy-2-phenylacetic acid using 1-hydroxybenzotriazole monohydrate and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride in DMF at room temp. for 15 h, followed by hydrogenolysis of the product over 20% Pd(OH)2 in MeOH under H for 2 h to give 2-{(2R)-2-((1R)-3,3-difluorocyclopentyl)-2-hydroxy-2-phenylacetyl}-2,7-diazaspiro[3.5]nonane (II). II in vitro showed IC50 of 180 and 1.9 for inhibiting the binding of [3H]-N-methylscopolamine to muscarine M2 and M3 receptor, resp. **Pharmaceutical** formulations contg. II were prepd.

IT **270257-50-6P**, cis-1-Benzyl-4-(tert-butoxycarbonylamino)-3-piperidinecarboxylic acid methyl ester
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of acylazetidine derivs. as selective inhibitors of muscarine M3 receptor for treating respiratory, urol. or digestive diseases)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

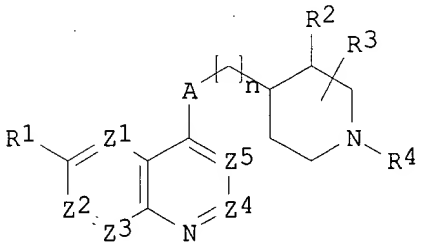
L18 ANSWER 22 OF 33 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:260272 HCAPLUS
DOCUMENT NUMBER: 132:293676
TITLE: Preparation of quinoline derivatives as antibacterial agents
INVENTOR(S): Davies, David Thomas; Markwell, Roger Edward; Pearson, Neil David; Takle, Andrew Kenneth
PATENT ASSIGNEE(S): Smithkline Beecham PLC, UK
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000021952	A1	20000420	WO 1999-EP7766	19991011
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9963395	A1	20000501	AU 1999-63395	19991011
EP 1121355	A1	20010808	EP 1999-950730	19991011
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002527434	T2	20020827	JP 2000-575858	19991011

PRIORITY APPLN. INFO.: GB 1998-22440 A 19981014
WO 1999-EP7766 W 19991011

OTHER SOURCE(S): MARPAT 132:293676
GI



I

AB The title compds. [I; one of Z1-Z5 = N, CR1a and the remainder are CH; R1 = OH, alkoxy, halo, etc.; R1a = H, R1; either R2 = H, and R3 is in 2- or 3-position and is H, alkyl, alkenyl, etc.; or when R3 is in the 2-position it may with R4 form (un)substituted alkylene; or R3 is in the 3-position and R2 and R3 together are a divalent residue :CR5R6 (wherein R5R6 = H, alkyl, alkenyl, etc.); R4 forms a group with R3 as above defined or is CH2R5 (R5 = alkyl, hydroxyalkyl, alkoxyalkyl, etc.); n = 0-2; A = NHCONH, NHCOO] and their **pharmaceutical** derivs., useful in treatment of bacterial infections in mammals, particularly in man, were prepd. Thus, reacting 6-methoxyquinoline-4-isocyanate with 1-heptyl-4-hydroxypiperidine afforded I [Z1-Z5 = CH; R1 = OMe; A = NHCOO; R2, R3 = H; R4 = heptyl; n = 0] which showed MIC of 8 .mu.g/mL against S. aureus Oxford, S. aureus Carter 37, and E. faecalis I.

IT **264229-37-0P 264229-38-1P 264229-39-2P**
264229-41-6P 264229-43-8P 264229-45-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of quinoline derivs. as antibacterial agents)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

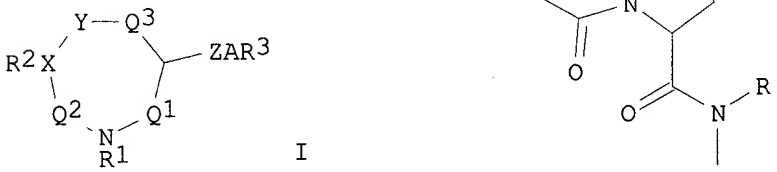
L18 ANSWER 23 OF 33 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:34889 HCAPLUS

DOCUMENT NUMBER: 132:93658
TITLE: Preparation of amino acid and peptide derivatives as microbial efflux pump inhibitors.
INVENTOR(S): Chamberland, Suzanne; Ishida, Yohei; Lee, Ving J.; Leger, Roger; Nakayama, Kiyoshi; Ohta, Toshiharu; Ohtsuka, Masami; Renau, Thomas W.; Watkins, William J.; Zhang, Zhijia J.
PATENT ASSIGNEE(S): Microcide Pharmaceuticals, Inc., USA; Daiich Pharmaceutical Co., Ltd.
SOURCE: PCT Int. Appl., 387 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000001714	A1	20000113	WO 1999-US14871	19990629
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6399629	B1	20020604	US 1998-108906	19980701
AU 9952073	A1	20000124	AU 1999-52073	19990629

PRIORITY APPLN. INFO.: US 1998-108906 A 19980701
US 1998-87514P P 19980601
WO 1999-US14871 W 19990629

OTHER SOURCE(S): MARPAT 132:93658
GI



I

AB A method for treating a microbial infection comprises administration of title compds. [I; Q1 = (CH2)n1; Q2 = (CH2)n2; Q3 = (CH2)n3; n1 = 0, 1; n2 = 0-3; n3 = 0-2; n1+n2+n3 = 1-4; X = N, CR2a, CR2b; R2a = H, alkyl; R2b = OH, F; Y = bond, S, O, NR23; R23 = H, alkyl; R1, R2 = H, C(:NR)R', C(:NR)NR'R'', etc.; R, R', R'' = H, alkyl; Z = bond, (CHR4)nCONR4, Q, etc.; R4 = H, alkyl, aralkyl; n = 0-3; A = bond, (CHR5)nX1(CHR5)n; X1 = O, S, bond, cycloalkylene, heterocycloalkylene; R5 = H, alkyl; R3 = H, (substituted) aryl, tetrahydronaphthyl, indanyl, thienyl, furyl, pyridyl, quinolyl, cycloalkyl, etc.; with provisos]. Thus, 1-(trans-4-aminomethyl-L-prolyl)-4-(3-chloro-2-methylphenyl)piperazine (soln. phase prepn. given) at 2.5 .mu.g/mL together with levofloxacin 0.25 .mu.g/mL gave 100% inhibition of Pseudomonas aeruginosa PAM1001 growth.

IT **254880-58-5P 254880-60-9P 254880-62-1P**

254880-64-3P 254880-66-5P 254880-67-6P
254880-69-8P 254880-71-2P 254880-73-4P
254880-75-6P 254880-76-7P 254880-77-8P
254880-78-9P 254880-79-0P 254880-80-3P
254880-81-4P 254880-82-5P 254880-83-6P
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254880-92-7P 254880-93-8P 254880-94-9P
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254881-17-9P 254881-19-1P 254881-21-5P
254881-22-6P 254881-23-7P 254881-24-8P
254881-25-9P 254881-27-1P 254881-28-2P
254881-29-3P 254881-30-6P 254881-31-7P
254881-32-8P 254881-33-9P 254881-40-8P
254881-41-9P 254881-43-1P 254881-44-2P
254881-45-3P 254881-49-7P 254881-52-2P
254884-01-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of amino acid and peptide derivs. as microbial efflux pump inhibitors)

IT **254883-94-8**
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of amino acid and peptide derivs. as microbial efflux pump inhibitors)

IT **254881-63-5P 254881-64-6P 254881-65-7P**
254881-66-8P 254881-67-9P 254881-68-0P
254881-69-1P 254881-70-4P 254881-71-5P
254881-72-6P 254881-73-7P 254881-74-8P
254881-75-9P 254881-76-0P 254881-78-2P
254881-80-6P 254881-81-7P 254881-82-8P
254881-83-9P 254881-84-0P 254881-85-1P
254881-86-2P 254881-87-3P 254881-88-4P
254881-91-9P 254881-98-6P 254882-03-6P
254882-04-7P 254882-05-8P 254882-10-5P
254882-11-6P 254882-12-7P 254882-18-3P
254882-19-4P 254882-20-7P 254882-21-8P
254882-22-9P 254882-23-0P 254882-24-1P
254882-25-2P 254882-26-3P 254882-29-6P
254882-30-9P 254882-31-0P 254882-32-1P
254882-36-5P 254882-38-7P 254882-39-8P
254882-40-1P 254882-43-4P 254882-45-6P
254882-46-7P 254882-47-8P 254882-49-0P
254882-50-3P 254882-51-4P 254882-52-5P
254882-53-6P 254882-57-0P 254882-58-1P
254882-62-7P 254882-66-1P 254882-70-7P
254882-74-1P 254882-78-5P 254882-79-6P
254882-80-9P 254882-81-0P 254882-82-1P
254882-83-2P 254882-84-3P 254882-85-4P
254882-86-5P 254882-87-6P 254882-90-1P
254882-91-2P 254882-92-3P 254882-93-4P
254882-94-5P 254883-01-7P 254883-03-9P
254883-04-0P 254883-05-1P 254883-12-0P
254883-13-1P 254883-14-2P 254883-15-3P
254883-17-5P 254883-18-6P 254883-19-7P
254883-20-0P 254883-21-1P 254883-22-2P

254883-23-3P 254883-26-6P 254883-30-2P
254883-35-7P 254883-37-9P 254883-40-4P
254883-41-5P 254883-44-8P 254883-59-5P
254883-61-9P 254883-62-0P 254883-70-0P
254883-75-5P 254884-03-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of amino acid and peptide derivs. as microbial efflux pump inhibitors)
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 24 OF 33 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:516440 HCAPLUS
DOCUMENT NUMBER: 131:272151
TITLE: Useful scaffolds and handles for creating diversity in the preparation of chemical libraries
AUTHOR(S): Royo, Miriam; Del Fresno, Montserrat; Frieden, Ariadna; Van Den Nest, Wim; Sanseverino, Marina; Alsina, Jordi; Kates, Steven A.; Barany, George; Albericio, Fernando
CORPORATE SOURCE: Department of Organic Chemistry, University of Barcelona, Barcelona, 08028, Spain
SOURCE: Reactive & Functional Polymers (1999), 41(1-3), 103-110
CODEN: RFPOF6; ISSN: 1381-5148
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Several scaffolds; having two, reactive, points and anchored to a solid support were prepd. These structures can display a wide range of pendant functionalities to give libraries of structurally diverse substances which can be used to search for new lead compds. and to achieve their subsequent optimization in a **medicinal** chem. program. The scaffolds are based upon diketopiperazine-, cis-aminoproline-, hydrazine-, and alkylenediamine-resins, which contain in all cases two amino functions blocked selectively with orthogonally removable protecting groups.
IT **174148-03-9**
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of scaffolds and handles for creating diversity in prepn. of chem. libraries)
IT **174148-03-9DP**, polystyrene-bound
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of scaffolds and handles for creating diversity in prepn. of chem. libraries)
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 25 OF 33 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:799995 HCAPLUS
DOCUMENT NUMBER: 130:52736
TITLE: Preparation of biarylalkanoic acids as cell adhesion inhibitors
INVENTOR(S): Durette, Philippe L.; Hagmann, William K.; Maccoss, Malcolm; Mills, Sander G.; Mumford, Richard A.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 96 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9853817	A1	19981203	WO 1998-US10951	19980529
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9877031	A1	19981230	AU 1998-77031	19980529
AU 726585	B2	20001109		
EP 1017382	A1	20000712	EP 1998-924988	19980529
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2001517245	T2	20011002	JP 1999-500938	19980529
US 6291511	B1	20010918	US 1999-359015	19990722

PRIORITY APPLN. INFO.:

US 1997-47856P	P	19970529
GB 1997-14316	A	19970707
US 1997-66831P	P	19971125
GB 1998-680	A	19980114
US 1998-85793	B1	19980528
WO 1998-US10951	W	19980529

OTHER SOURCE(S): MARPAT 130:52736

AB Compds. R1YNR2CR3R4CONR5CR6R7X [R1 = (un)substituted alkyl, alkenyl, alkynyl, a cyclic group Cy, Cy-alkyl, Cy-alkenyl, Cy-alkynyl; R2, R3 independently are H or R1; or R2 and R3 together form a ring; R4, R7 independently are H, (un)substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl; or R3 and R4 together form a ring; R5 = H or (un)substituted alkyl or Cy; R6 = diarylalkyl, -alkenyl, or -alkynyl; X = CO2H, PO3H2, PH(O)OH, SO2H, SO3H or ester derivs., carbamoyl group, or 5-tetrazolyl; Y = CO, OCO, NHCO or iminocarbonyl group, SO2, P(O)(ORi) (Ri =alkyl, alkenyl, alkynyl, aryl), COCO] were prepd. as cell adhesion inhibitors. **Pharmaceutical** compns. are described. Thus, N-(3,5-dichlorobenzenesulfonyl)-L-prolyl-L-4-(4-fluorophenyl)phenylalanine was prepd. by coupling of N-(3,5-dichlorobenzenesulfonyl)-L-proline with 4-iodo-L-phenylalanine and reaction with 4-fluorobenzeneboronic acid.

IT **217326-51-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of peptidyl biarylalkanoic acids as cell adhesion inhibitors)

IT **217325-48-9P 217325-49-0P 217325-50-3P 217325-51-4P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of peptidyl biarylalkanoic acids as cell adhesion inhibitors)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 26 OF 33 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:484582 HCAPLUS
DOCUMENT NUMBER: 129:211233
TITLE: 3-Carbomethoxy fentanyl: synthesis, **pharmacology** and conformational analysis
AUTHOR(S): Micovic, I. V.; Ivanovic, M. D.; Vuckovic, S.; Jovanovic-Micic, D.; Beleslin, D.; Dosen-Micovic, Lj.; Kiricojevic, V. D.
CORPORATE SOURCE: Faculty of Chemistry, University of Belgrade, Belgrade, YU-550 11001, Yugoslavia
SOURCE: Heterocyclic Communications (1998), 4(2), 171-179
CODEN: HCOMEX; ISSN: 0793-0283
PUBLISHER: Freund Publishing House Ltd.
DOCUMENT TYPE: Journal

LANGUAGE: English

AB The synthesis of a novel analog of fentanyl, 3-carbomethoxy fentanyl or iso-carfentanil has been accomplished in five steps, by simple and efficient route, starting from phenethyl amine and Me acrylate. Both (.+-.) cis and (.+-.) trans isomers of 3-carbomethoxy fentanyl were obtained in pure form and tested **pharmacol.** for the central analgesic activity. Preliminary results (rat-withdrawal test) revealed significant but substantially reduced potency of both isomers, the trans in particular, compared to carfentanil. The computational (mol. mechanics) search of the conformational space low energy regions of (.+-.) cis and (.+-.) trans isomers revealed the difference in their conformational mobility. Besides being more conformationally flexible trans isomer has unfavorable orientation of the 4-N-phenylpropanamide group compared to the other active analogs of fentanyl. This is believed to be the reason of its reduced potency relative to fentanyl.

IT **203639-44-5P 203639-45-6P**, trans-3-Carbomethoxyfentanyl
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis, analgesic activity and conformational anal. of 3-carbomethoxy fentanyl)

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 27 OF 33 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:268513 HCAPLUS
DOCUMENT NUMBER: 128:321945
TITLE: Preparation of peptide analogs as inhibitors of serine proteases, particularly hepatitis C virus NS3 protease
INVENTOR(S): Tung, Roger D.; Harbeson, Scott L.; Deininger, David D.; Murcko, Mark A.; Bhisetti, Govinda Rao; Farmer, Luc J.
PATENT ASSIGNEE(S): Vertex Pharmaceuticals Inc., USA; Tung, Roger D.; Harbeson, Scott L.; Deininger, David D.; Murcko, Mark A.; Bhisetti, Govinda Rao; Farmer, Luc J.
SOURCE: PCT Int. Appl., 128 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9817679	A1	19980430	WO 1997-US18968	19971017
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
ZA 9709327	A	19980511	ZA 1997-9327	19971017
AU 9851477	A1	19980515	AU 1998-51477	19971017
AU 719984	B2	20000518		
EP 932617	A1	19990804	EP 1997-946273	19971017
EP 932617	B1	20020116		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 9712544	A	19991019	BR 1997-12544	19971017
CN 1238780	A	19991215	CN 1997-180151	19971017
NZ 335276	A	20000929	NZ 1997-335276	19971017

JP 2001502694	T2	20010227	JP 1998-519568	19971017
EP 1136498	A1	20010926	EP 2001-109433	19971017
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
AP 1019	A	20011016	AP 1999-1512	19971017
W: GH, KE, LS, MW, SD, SZ, UG, ZW				
AT 212037	E	20020215	AT 1997-946273	19971017
ES 2169880	T3	20020716	ES 1997-946273	19971017
NO 9901832	A	19990617	NO 1999-1832	19990416
US 6265380	B1	20010724	US 1999-293247	19990416
KR 2000049263	A	20000725	KR 1999-703372	19990417
US 2002032175	A1	20020314	US 2001-875390	20010606

PRIORITY APPLN. INFO.: US 1996-28290P P 19961018
EP 1997-946273 A3 19971017
WO 1997-US18968 W 19971017
US 1999-293247 A 19990416

OTHER SOURCE(S): MARPAT 128:321945

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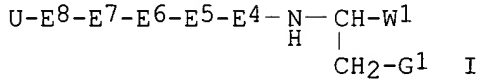

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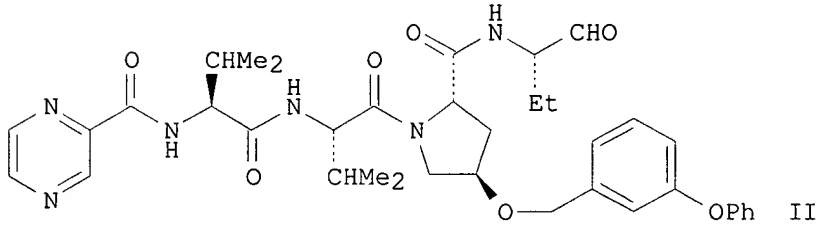

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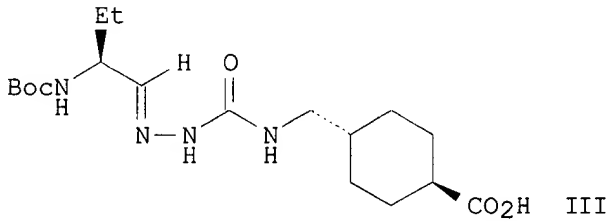


III

AB The present invention relates to compds. I [G1 = SH, OH, SMe, alkenyl, alkynyl, CF3, C1-2 alkoxy, C1-2 alkylthio, (un)substituted C1-3 alkyl; W1 = COCF2CH2N(G4)U, CHO, COG2, COCF2CF3, COCOG2, COCO2G2, B(Q1)2; G2 = alkyl, aryl, aralkyl, (un)substituted mono-, bi-, or tricyclic heterocycle; G4 = alky, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkenyl, aryl, aralkyl, aralkenyl, etc.; Q1 = OH, alkoxy, aryloxy, or Q1-Q1 form a 5-7 membered ring; U = H, G9CO, G9SO2, G9COCO, (G9)2NCOCO, (G9)2NSO2, (G9)2NCO, G9O2C; G9 = H, alkyl, carboxyalkyl, alkenyl, aryl, aralkyl, aralkenyl, cycloalkyl, heterocycloalkyl, etc; or G9-G9 form a ring; E4 = bond, .alpha.-amino acid residue, heterocyclic amino acid; E5-E8 = independently bond, amino acid residue; 1-2 peptide bonds between E5-E8 may be reduced], methods and **pharmaceutical**

compns. for inhibiting proteases, particularly serine proteases, and more particularly HCV NS3 proteases. The compds., and the compns. and methods that utilize them, can be used, either alone or in combination to inhibit viruses, particularly HCV virus. Thus, peptide aldehyde II was prepd. using solid-phase methods on a benzhydrylamine resin and tert-butoxycarbonyl (Boc) and 9-fluorenylmethoxycarbonyl (Fmoc) protection starting from protected hydrazone III. Nearly 200 compds. I were prepd. and tested for hepatitis C virus NS3 protease inhibitory activity, with II exhibiting Ki <1 .mu.M in an in vitro assay.

IT **207001-40-9P 207001-41-0P 207001-42-1P**
207001-43-2P 207001-44-3P 207001-45-4P
207001-46-5P 207001-47-6P 207001-49-8P
207001-51-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of peptide analogs as hepatitis C virus NS3 protease inhibitors)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 28 OF 33 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:122612 HCAPLUS
DOCUMENT NUMBER: 128:192526
TITLE: The synthesis, **pharmacological** evaluation and conformational analysis of-(.+-.)-cis- and (.+-.)-trans-3-carbomethoxyfentanyl - "iso-carfentanil"
AUTHOR(S): Micovic, I. V.; Ivanovic, M. D.; Vuckovic, S.; Jovanovic-Micic, D.; Beleslin, D.; Dosen-Micovic, Lj.; Kiricojevic, V. D.
CORPORATE SOURCE: Faculty of Chemistry, University of Belgrade, Belgrade, YU-11001, Yugoslavia
SOURCE: Journal of the Serbian Chemical Society (1998), 63(2), 93-112
CODEN: JSCSEN; ISSN: 0352-5139
PUBLISHER: Serbian Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A novel analog of fentanyl, 3-carbomethoxyfentanyl, or isocarfentanyl, was synthesized by a simple and efficient route. In the first step phenethylamine was condensed with two equiv. of Me acrylate to afford an amino diester in quant. yield. Dieckmann cyclization of this intermediate yielded 3-carbomethoxy-N-phenethyl-4-piperidone in .apprx. 80% yield, after mild hydrolysis. Condensation of this .beta.-keto ester with aniline in acetic acid gave a stable enamine (70% yield) which was then reduced with NaBH3CN in methanol at pH .apprxeq. 5, to yield 4-anilino-3-carbomethoxy-N-phenethyl piperidine, quant. This intermediate was obtained as a 50:50 mixt. of the desired (.+-.)-cis and (.+-.)-trans isomers. After the mixt. of diastereoisomers was sepd. on a neutral aluminum oxide column, the pure isomers were acylated with propionyl chloride, thus completing the synthesis of 3-carbomethoxyfentanyl. The relative stereochem. was detd. by 1H-NMR spectroscopy. These compds. present regioisomer of carfentanil, one of the most potent narcotic analgesics known to date. Preliminary **pharmacol**. evaluation (tail-withdrawal test in rats) revealed substantially reduced potency of both diastereoisomers, the (.+-.)-trans-isocarfentanyl in particular, compared to carfentanil. The computational (mol. mechanics) search of the low energy regions of the conformational space of the cis-isocarfentanyl and trans-isocarfentanyl isomers revealed the difference in their conformational mobility. Besides being more conformationally flexible, the trans isomer has unfavorable orientation of the 4-N-phenylpropanamide

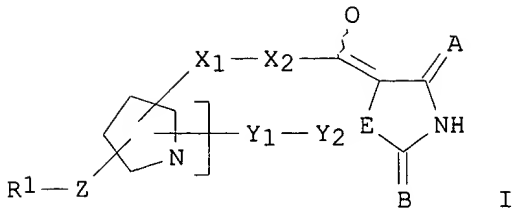
group compared to the other active analogs of fentanyl. This is believed to be the reason of its reduced potency relative to fentanyl.

IT **203639-44-5P 203639-45-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and **pharmacol.** evaluation and conformational anal. of isocarfentanil)

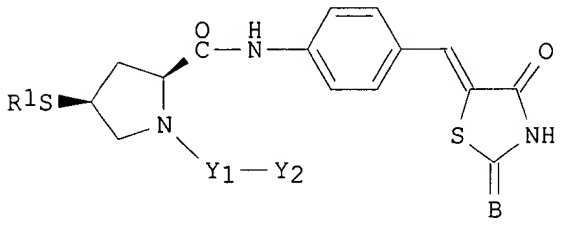
L18 ANSWER 29 OF 33 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:240627 HCAPLUS
DOCUMENT NUMBER: 126:225294
TITLE: Preparation of pyrrolidine derivatives as phospholipase A2 inhibitors
INVENTOR(S): Ohtani, Mitsuaki; Kato, Toshiyuki; Watanabe, Fumihiko; Seno, Kaoru
PATENT ASSIGNEE(S): Shionogi and Co., Ltd., Japan; Ohtani, Mitsuaki; Kato, Toshiyuki; Watanabe, Fumihiko; Seno, Kaoru
SOURCE: PCT Int. Appl., 129 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9705135	A1	19970213	WO 1996-JP2079	19960725
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA				
CA 2227829	AA	19970213	CA 1996-2227829	19960725
AU 9665308	A1	19970226	AU 1996-65308	19960725
AU 707537	B2	19990715		
EP 848004	A1	19980617	EP 1996-925076	19960725
EP 848004	B1	20030402		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
CN 1197458	A	19981028	CN 1996-197208	19960725
CN 1064682	B	20010418		
BR 9609744	A	19990302	BR 1996-9744	19960725
US 5955616	A	19990921	US 1998-11404	19980128

PRIORITY APPLN. INFO.: JP 1995-194648 A 19950731
WO 1996-JP2079 W 19960725
OTHER SOURCE(S): MARPAT 126:225294
GI



I



II

AB The title compds. [I; R1 = H, (un)substituted alkyl, alkenyl, or aralkyl, etc.; A, B, E = O, S; X1 = CO, CONH, CH2NHSO2, etc.; X2 = (un)substituted arylene or indolediyl, single bond; D = H, hydroxyalkyl; Y1 = (CH2)mCO, (CH2)nNHCO, etc.; m, n = 0-3; Y2 = H, alkyl, (un)substituted alkenyl, etc.; Z = S, SO, O, NH, CONH, CONHCH2, single bond] and **pharmaceutically** acceptable salts thereof are prepd. I have the activity of inhibiting the prodn. of prostaglandin E2 by inhibiting intracellular phospholipase A2. I, having the activity of inhibiting the prodn. of prostaglandin E2 by inhibiting intracellular phospholipase A2, are useful for prevention and treatment of rheumatoid arthritis, asthma, allergic rhinitis, and related diseases. Thus, the title compd. (II; R1 = C6H4CH2, Y2-Y1 = C6H4CO, B = S), which was prepd. by 13 step reactions, showed IC50 of 7.2 .mu.M cPLA2 inhibitory activity.

IT **188110-92-1P 188110-95-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of pyrrolidine derivs. as phospholipase A2 inhibitors)

L18 ANSWER 30 OF 33 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:219832 HCAPLUS
DOCUMENT NUMBER: 126:305772
TITLE: New hetero-oligomeric peptide nucleic acids with improved binding properties to complementary DNA
AUTHOR(S): Jordan, Stephan; Schwemler, Christoph; Kosch, Winfried; Kretschmer, Axel; Stropp, Udo; Schwenner, Eckhardt; Mielke, Burkhard
CORPORATE SOURCE: Bayer AG, Central Research, Leverkusen, D-51368, Germany
SOURCE: Bioorganic & Medicinal Chemistry Letters (1997), 7(6), 687-690
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Hetero-oligomeric PNAs consisting of new monomeric building blocks

L-trans-I, L-cis-I, D-trans-I, II, and III (X = O) and various amts. of N-(2-aminoethyl)glycine (IV) have been synthesized by solid-phase chem. Some of these new compds. show stronger binding to complementary DNA than the original PNAs, and are consequently very interesting candidates as antisense compds. for applications in **therapy** and in diagnostics.

IT **176230-60-7P 176483-95-7P 189253-82-5P 189253-83-6P 189253-84-7P 189253-85-8P 189253-87-0P**
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of new hetero-oligomeric peptide nucleic acids with improved binding properties to complementary DNA)

IT **168263-84-1 185304-25-0 189253-88-1**
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of new hetero-oligomeric peptide nucleic acids with improved binding properties to complementary DNA)

L18 ANSWER 31 OF 33 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:281618 HCAPLUS
DOCUMENT NUMBER: 124:344113
TITLE: Preparation of nucleic acid-binding oligomers as **drugs** and diagnostic agents.
INVENTOR(S): Schwemler, Christoph; Poetter, Thorsten; Mielke, Burkhard; Schwenner, Eckhard; Kretschmer, Axel; Stropp, Udo; Kosch, Winfried; Duerr, Hanshoerg
PATENT ASSIGNEE(S): Bayer A.-G., Germany
SOURCE: Ger. Offen., 12 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 4427980	A1	19960215	DE 1994-4427980	19940808
EP 700928	A1	19960313	EP 1995-111735	19950726
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, NL, PT, SE				
AU 9528321	A1	19960222	AU 1995-28321	19950801
US 5955571	A	19990921	US 1995-509913	19950801
JP 08059692	A2	19960305	JP 1995-216573	19950803
CA 2155496	AA	19960209	CA 1995-2155496	19950804

PRIORITY APPLN. INFO.: DE 1994-4427980 19940808

AB M[NHGAN[D(CH2)mB]K[QCH2CH2N(COCH2B)CH2CO]r]sL [A = (CH2)n, CO; B = (un)natural nucleobase (deriv); D = (CO)p; E, G = CHR; R = H, (protected) amino acid residue; E and G may be connected by a (substituted) alkylene chain; K = CO, SO2, CH2; L = H, carrier system, reporter ligand, solubilizing group; Q = NH, O, S, NR; m = 0-3; n = 0-4; p = 0-2; r = 0, 1; s = 1-30], were prepd. Thus, H-T1-T2-T1-T2-T1-T2-T1-T2-Lys-NH2 [T1 = aminoethylglycine thymine residue; T2 = L-trans-4-amino-N-[(thymin-1-yl)acetyl]proline residue], prepd. by solid phase synthesis using BOC methodol. on MBHA resin, was stable to proteinase K and S1 nuclease while hybridizing very strongly with single stranded DNA.

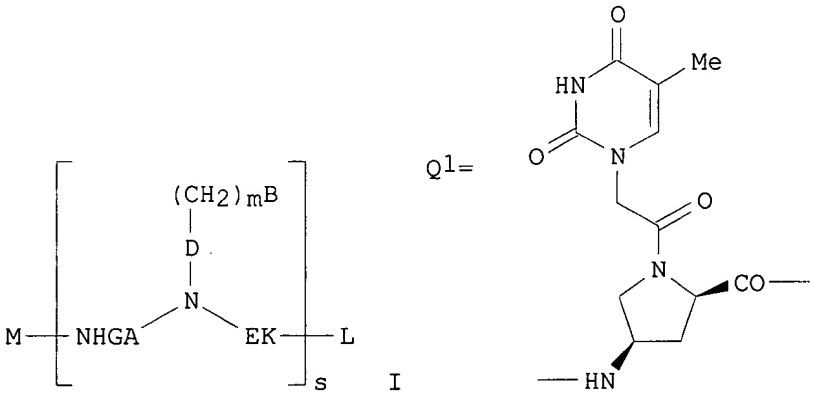
IT **176230-60-7P 176483-95-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of nucleic acid-binding oligomers as **drugs** and diagnostic agents)

L18 ANSWER 32 OF 33 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:820572 HCAPLUS
DOCUMENT NUMBER: 123:228912

TITLE: Preparation of nucleic acid-binding oligomers with amino acid-containing backbones and nucleobase-containing side chains.
INVENTOR(S): Loebberding, Antonius; Mielkde, Burkhard; Schwemler, Christoph; Schwenner, Eckhardt; Stropp, Udo; Springer, Wolfgang; Kretschmer, Axel; Poetter, Thorsten
PATENT ASSIGNEE(S): Bayer A.-G., Germany
SOURCE: Ger. Offen., 23 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 4331012	A1	19950316	DE 1993-4331012	19930913
AU 9471543	A1	19950323	AU 1994-71543	19940829
AU 676349	B2	19970306		
EP 646595	A1	19950405	EP 1994-113569	19940831
EP 646595	B1	19981104		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, NL, SE				
AT 172984	E	19981115	AT 1994-113569	19940831
ES 2124345	T3	19990201	ES 1994-113569	19940831
US 5623049	A	19970422	US 1994-300884	19940906
JP 07118243	A2	19950509	JP 1994-239644	19940908
CA 2131755	AA	19950314	CA 1994-2131755	19940909

PRIORITY APPLN. INFO.: DE 1993-4331012 19930913
OTHER SOURCE(S): MARPAT 123:228912
GI



AB Title compds. [I; A = (CH2)n, CO; B = (un)natural nucleoside base; D = (CO)p; E, G = CHR; R = H, (un)natural amino acid residue; E and G may be bonded to each other by (CH2)n; K = CO, SO2, CH2; M, L = H, carrier system, reporter ligand, solubilizing group; m = 0-3; n = 0-4; p, q = 0-2; s = 1-30], were prepd. Thus, H-(Q1)8-Ala-OH, prepd. by solid phase synthesis on phenylacetamidomethyl resin, showed concn.-dependent and sequence-selective binding to double-stranded DNA and showed stability to various proteases.

IT **168263-94-3P 168263-95-4P 168263-96-5P**
168263-97-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); SPN (Synthetic

preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of nucleic acid-binding oligomers with amino acid-contg. backbones and nucleobase-contg. side chains)

IT **168263-80-7P 168263-82-9P 168263-83-0P**
168263-84-1P 168263-87-4P 168263-91-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of nucleic acid-binding oligomers with amino acid-contg. backbones and nucleobase-contg. side chains)

L18 ANSWER 33 OF 33 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1990:441332 HCAPLUS
DOCUMENT NUMBER: 113:41332
TITLE: Preparation of peptide amides as human immunodeficiency virus inhibitors
INVENTOR(S): Handa, Balraj Krishan; Machin, Peter James; Martin, Joseph Armstrong; Redshaw, Sally; Thomas, Gareth John
PATENT ASSIGNEE(S): Hoffmann-La Roche, F., und Co. A.-G., Switz.
SOURCE: Eur. Pat. Appl., 69 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 346847	A2	19891220	EP 1989-110717	19890613
EP 346847	A3	19911023		
EP 346847	B1	19940511		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
US 5157041	A	19921020	US 1989-362621	19890605
ZA 8904285	A	19900228	ZA 1989-4285	19890606
AU 8936130	A1	19891214	AU 1989-36130	19890607
AU 624144	B2	19920604		
HU 51254	A2	19900428	HU 1989-2903	19890607
HU 205898	B	19920728		
DK 8902863	A	19891214	DK 1989-2863	19890612
DK 172747	B1	19990628		
NO 8902407	A	19891214	NO 1989-2407	19890612
NO 175715	B	19940815		
NO 175715	C	19941123		
JP 02042048	A2	19900213	JP 1989-149265	19890612
JP 2515019	B2	19960710		
KR 9705905	B1	19970422	KR 1989-8040	19890612
FI 8902881	A	19891214	FI 1989-2881	19890613
FI 95693	B	19951130		
FI 95693	C	19960311		
AT 105549	E	19940515	AT 1989-110717	19890613
ES 2052815	T3	19940716	ES 1989-110717	19890613
US 5446161	A	19950829	US 1992-916812	19920720
US 5554756	A	19960910	US 1995-391380	19950217
US 5652369	A	19970729	US 1995-394523	19950406
US 5620987	A	19970415	US 1995-398478	19950410

PRIORITY APPLN. INFO.:
GB 1988-13940 A 19880613
GB 1989-8035 A 19890410
US 1989-362621 A3 19890605
EP 1989-110717 A 19890613
US 1992-916812 A3 19920720

OTHER SOURCE(S): MARPAT 113:41332
AB R1R2NCHR3CONHCHR4CR5R6CH2N(:O)nR7CHR8R9 [I; R1 = alkoxycarbonyl, aralkoxycarbonyl, (ar)alkanoyl, cycloalkylcarbonyl, aroyl,

heterocyclylcarbonyl, alkylsulfonyl, etc.; R2 = H; R1R2N = cyclic arom. imide; R3 = (cyclo)alkyl, (aryl)alkyl, aryl, heterocyclylalkyl, cyanoalkyl, etc; R4 = alkyl, cycloalkyl(alkyl), aryl(alkyl); R5 = H; R6 = OH; R5R6 = :O; R7R8 = (un)substituted (CH2)3, (CH2)4, with 1 CH2 optionally replaced by NH, N(acyl), S, etc., optionally carrying 1 fused cycloalkane or (hetero)arom. ring; R9 = alkoxycarbonyl, monoalkylcarbamoyl, CONHCHR10CONHR11; R10, R11 = alkyl; n = 0, 1] and their **pharmaceutically** acceptable salts were prepd., e.g., by coupling amines H2NCHR4CR5R6CH2NR7CHR8R9 with acids R1R2NCHR3CO2H. Thus, N1-isobutyl-L-isoleucylamide (prepn. given) was coupled with Z-proline succinimide ester (Z = benzyloxycarbonyl), the resulting dipeptide was deprotected and coupled with (Z-phenylalanyl)methyl bromide, the intermediate tripeptide reduced by NaBH4 in EtOH, deprotected, and coupled with Z-Asn-OH to give N2-[N-[3(S)-[(Z-asparaginyl)amino]-2(R,S)-hydroxy-4-phenylbutyl]-L-prolyl]-N1-isobutyl-L-isoleucylamide. One (unspecified) of 2 isomers of the latter in vitro inhibited human immunodeficiency virus protease with an IC50 of 0.13 .mu.M. IC50 values reported for 7 other I ranged from 0.01-0.87 .mu.M.

IT **128019-81-8P 128019-86-3P 128019-87-4P**
128019-88-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and reaction of, in prepn. of HIV protease inhibitor)

IT **128019-82-9P 128019-94-3P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. of, as HIV protease inhibitor)

=>
=>

=> select hit rn l18 1-33
E# OR SYSTEM LIMIT REACHED WHILE PROCESSING ANSWER 23
E1 THROUGH E999 ASSIGNED

=> fil reg
FILE 'REGISTRY' ENTERED AT 13:41:02 ON 18 APR 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 17 APR 2003 HIGHEST RN 503414-07-1
DICTIONARY FILE UPDATES: 17 APR 2003 HIGHEST RN 503414-07-1

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

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=> d his l18-

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L18          33 S L17 NOT L12

     FILE 'HCAPLUS' ENTERED AT 13:39:57 ON 18 APR 2003
               SELECT HIT RN L18 1-33

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L19          999 S E1-E999

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L20         1197 S L19 OR E1-E223

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950 1000 1050 1100 1150 1197

L20  ANSWER 1 OF 1197  REGISTRY  COPYRIGHT 2003 ACS
RN   503172-97-2  REGISTRY
CN   INDEX NAME NOT YET ASSIGNED
FS   STEREOSEARCH
MF   C21 H20 F3 N5 O3 . x C2 H F3 O2
SR   CA
LC   STN Files:   CAPLUS

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     CRN  503172-96-1
     CMF  C21 H20 F3 N5 O3

Absolute stereochemistry.
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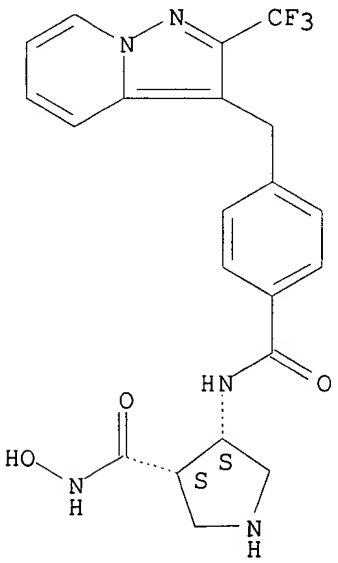

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     CRN  76-05-1
     CMF  C2 H F3 O2
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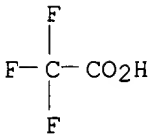
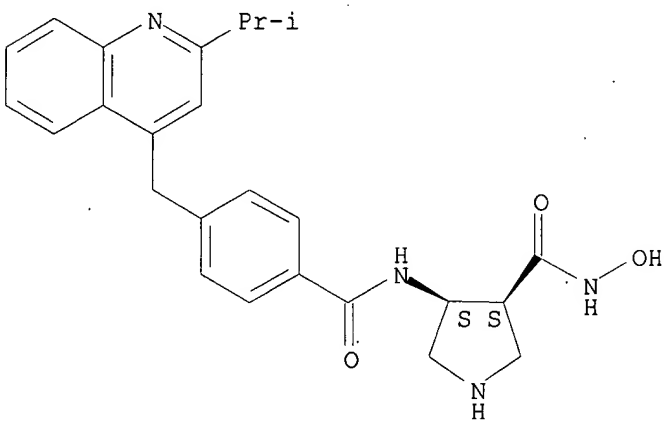


1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L20 ANSWER 50 OF 1197 REGISTRY COPYRIGHT 2003 ACS
RN **503170-38-5** REGISTRY
CN INDEX NAME NOT YET ASSIGNED
FS STEREOSEARCH
MF C25 H28 N4 O3
SR CA
LC STN Files: CAPLUS

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

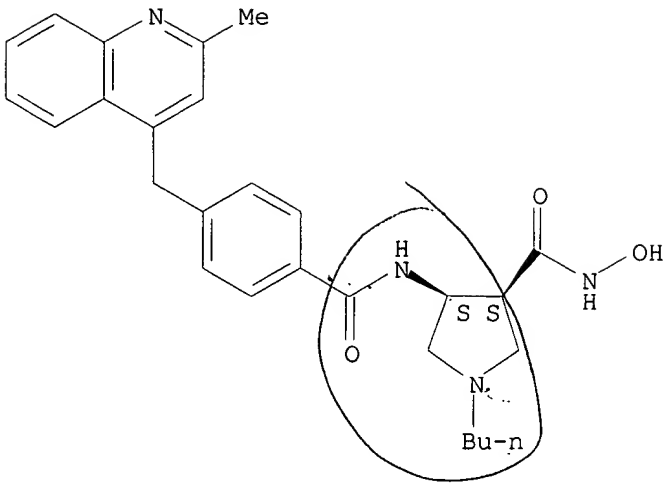
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L20 ANSWER 100 OF 1197 REGISTRY COPYRIGHT 2003 ACS
RN **503169-78-6** REGISTRY
CN 3-Pyrrolidinecarboxamide, 1-butyl-N-hydroxy-4-[[4-[(2-methyl-4-quinolinyl)methyl]benzoyl]amino]-, (3S,4S)-, trifluoroacetate (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C27 H32 N4 O3 . x C2 H F3 O2
SR CA
LC STN Files: CAPLUS

CM 1

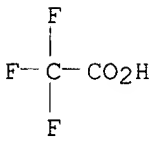
CRN 503169-77-5
CMF C27 H32 N4 O3

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2



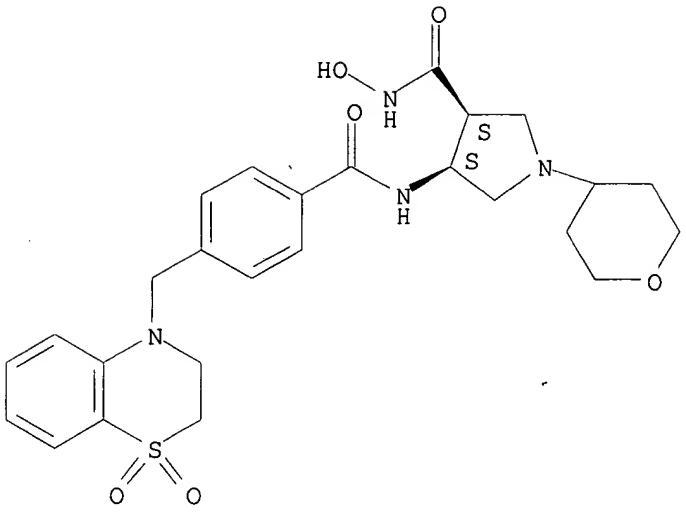
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L20 ANSWER 150 OF 1197 REGISTRY COPYRIGHT 2003 ACS
RN **503168-92-1** REGISTRY
CN 3-Pyrrolidinecarboxamide, 4-[[4-[(2,3-dihydro-1,1-dioxido-4H-1,4-benzothiazin-4-yl)methyl]benzoyl]amino]-N-hydroxy-1-(tetrahydro-2H-pyran-4-yl)-, (3S,4S)-, trifluoroacetate (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C26 H32 N4 O6 S . x C2 H F3 O2
SR CA
LC STN Files: CAPLUS

CM 1

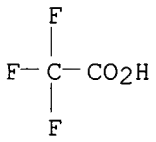
CRN 503168-91-0
CMF C26 H32 N4 O6 S

Absolute stereochemistry.



CM 2

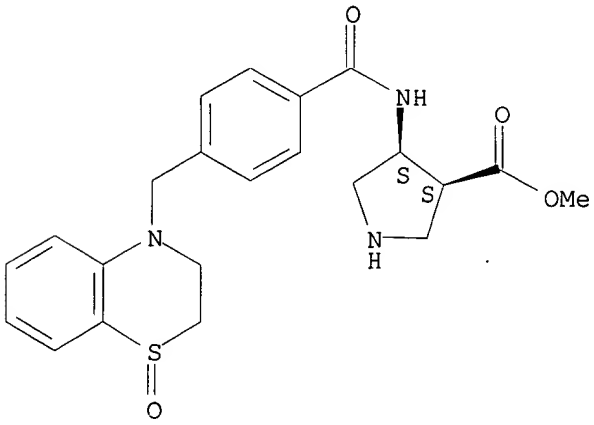
CRN 76-05-1
CMF C2 H F3 O2



1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L20 ANSWER 200 OF 1197 REGISTRY COPYRIGHT 2003 ACS
RN **503168-41-0** REGISTRY
CN INDEX NAME NOT YET ASSIGNED
FS STEREOSEARCH
MF C22 H25 N3 O4 S
SR CA
LC STN Files: CAPLUS

Absolute stereochemistry.

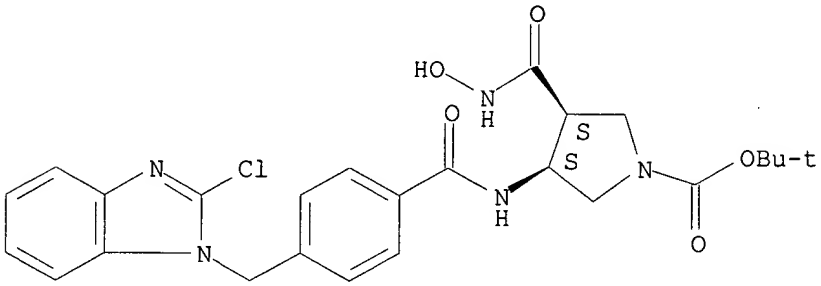


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L20 ANSWER 250 OF 1197 REGISTRY COPYRIGHT 2003 ACS
RN **503167-07-5** REGISTRY
CN INDEX NAME NOT YET ASSIGNED
FS STEREOSEARCH
MF C25 H28 Cl N5 O5
SR CA
LC STN Files: CAPLUS

Absolute stereochemistry.

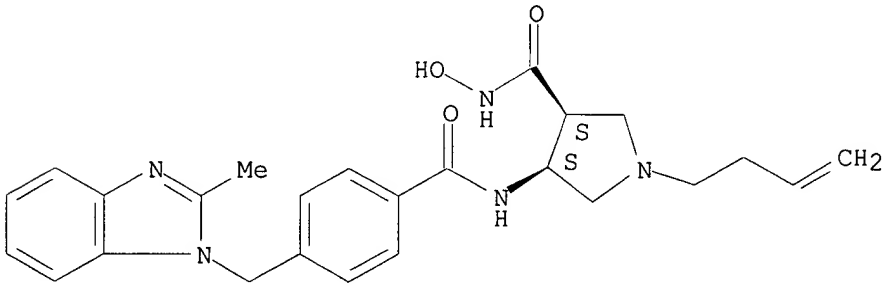


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L20 ANSWER 300 OF 1197 REGISTRY COPYRIGHT 2003 ACS
RN **503166-16-3** REGISTRY
CN INDEX NAME NOT YET ASSIGNED
FS STEREOSEARCH
MF C25 H29 N5 O3
SR CA
LC STN Files: CAPLUS

Absolute stereochemistry.



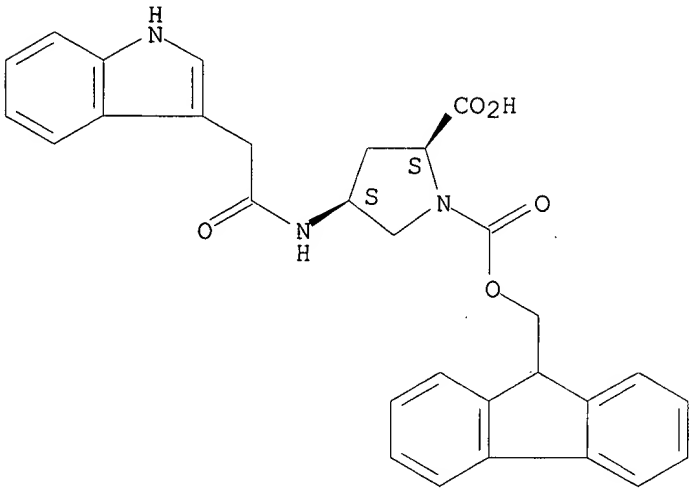
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

L20 ANSWER 350 OF 1197 REGISTRY COPYRIGHT 2003 ACS
RN **458547-05-2** REGISTRY
CN 1,2-Pyrrolidinedicarboxylic acid, 4-[(1H-indol-3-ylacetyl)amino]-,

1-(9H-fluoren-9-ylmethyl) ester, (2S,4S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C30 H27 N3 O5
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Absolute stereochemistry.



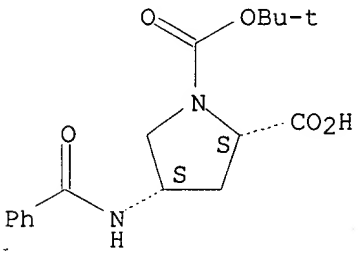
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:232914

L20 ANSWER 400 OF 1197 REGISTRY COPYRIGHT 2003 ACS
RN **401564-27-0** REGISTRY
CN 1,2-Pyrrolidinedicarboxylic acid, 4-(benzoylamino)-, 1-(1,1-dimethylethyl) ester, (2S,4S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C17 H22 N2 O5
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

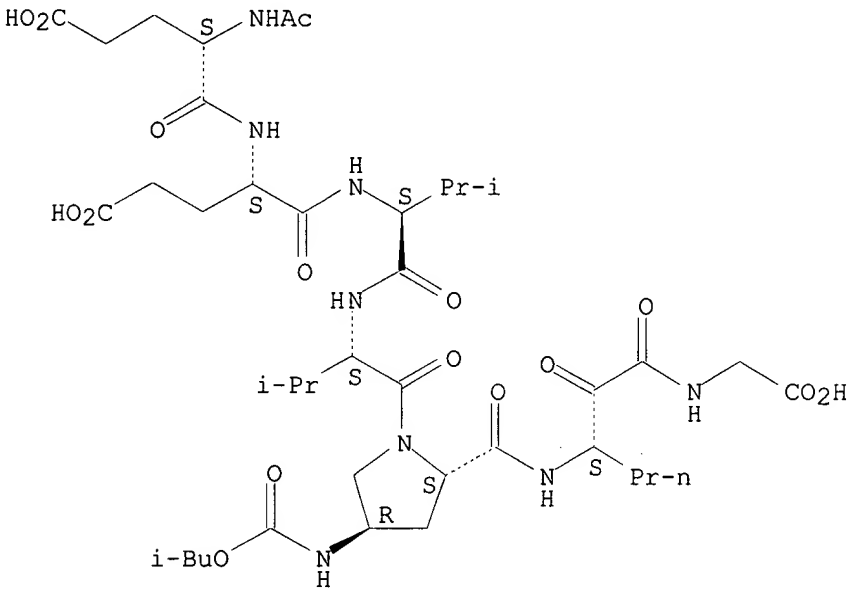
1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 136:200479

L20 ANSWER 450 OF 1197 REGISTRY COPYRIGHT 2003 ACS
RN **393522-99-1** REGISTRY
CN Glycine, N-acetyl-L-.alpha.-glutamyl-L-.alpha.-glutamyl-L-valyl-L-valyl-(4R)-4-[[(2-methylpropoxy)carbonyl]amino]-L-prolyl-(3S)-3-amino-2-oxohexanoyl- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C40 H64 N8 O16
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.



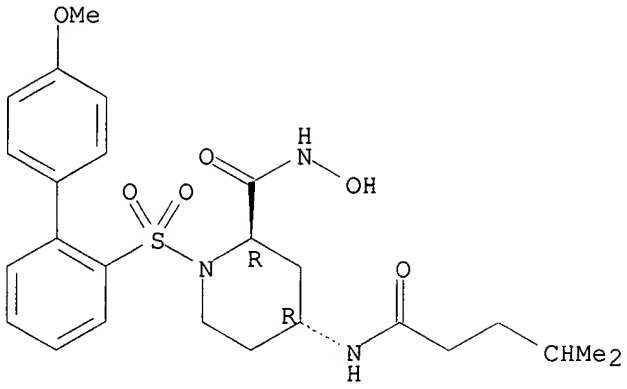
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 136:151440

L20 ANSWER 500 OF 1197 REGISTRY COPYRIGHT 2003 ACS
RN **374537-14-1** REGISTRY
CN 2-Piperidinecarboxamide, N-hydroxy-1-[(4'-methoxy[1,1'-biphenyl]-2-yl)sulfonyl]-4-[(4-methyl-1-oxopentyl)amino]-, (2R,4R)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN (2R,4R)-2-Hydroxyaminocarbonyl-1-[(2-(4-methoxyphenyl)benzene)sulfonyl]-4-(4-methylpentanoylamino)piperidine
FS STEREOSEARCH
MF C25 H33 N3 O6 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.



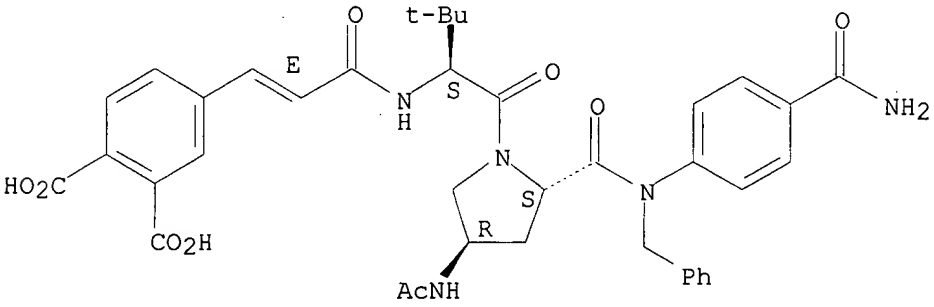
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 135:371642

L20 ANSWER 550 OF 1197 REGISTRY COPYRIGHT 2003 ACS
RN **371920-07-9** REGISTRY
CN L-Prolinamide, N-[(2E)-3-(3,4-dicarboxyphenyl)-1-oxo-2-propenyl]-3-methyl-L-valyl-4-(acetylamino)-N-[4-(aminocarbonyl)phenyl]-N-(phenylmethyl)-, (4R)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C38 H41 N5 O9
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.
Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

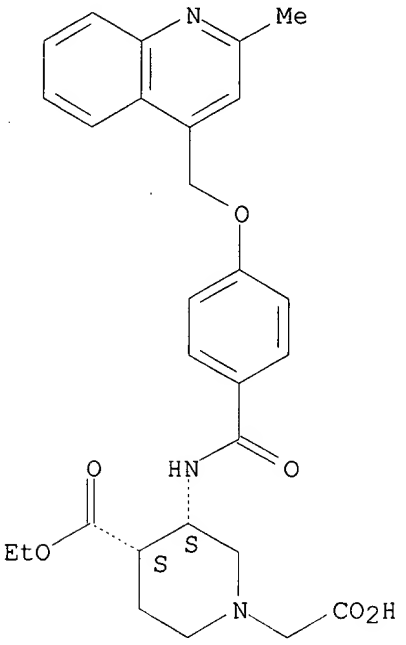
1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 135:339205

L20 ANSWER 600 OF 1197 REGISTRY COPYRIGHT 2003 ACS
RN **362490-00-4** REGISTRY
CN 1-Piperidineacetic acid, 4-(ethoxycarbonyl)-3-[[4-[(2-methyl-4-quinolinyl)methoxy]benzoyl]amino]-, (3S,4S)- (9CI) (CA INDEX NAME)

FS STEREOSEARCH
MF C28 H31 N3 O6
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 135:257169

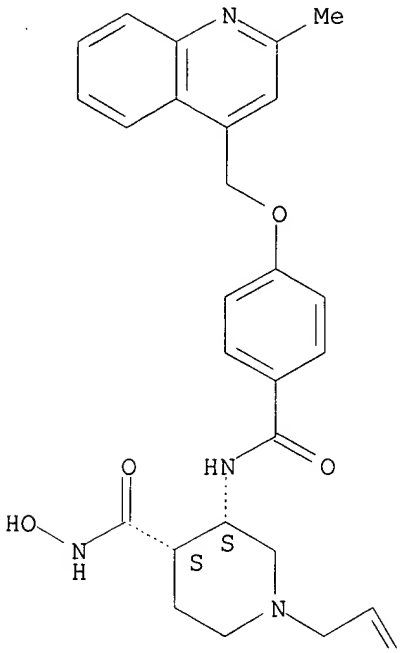
L20 ANSWER 650 OF 1197 REGISTRY COPYRIGHT 2003 ACS
RN **362488-09-3** REGISTRY
CN 4-Piperidinecarboxamide, N-hydroxy-3-[[4-[(2-methyl-4-quinolinyl)methoxy]benzoyl]amino]-1-(2-propenyl)-, (3S,4S)-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C27 H30 N4 O4 . 2 C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

CM 1

CRN 362488-08-2
CMF C27 H30 N4 O4

Absolute stereochemistry.

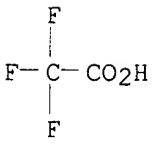
PAGE 1-A



PAGE 2-A

CM 2

CRN 76-05-1
CMF C2 H F3 O2



1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 135:257169

L20 ANSWER 700 OF 1197 REGISTRY COPYRIGHT 2003 ACS
RN **362487-23-8** REGISTRY
CN 4-Piperidinecarboxamide, N-hydroxy-3-[[4-[(2-methyl-4-quinolinyl)methoxy]benzoyl]amino]-1-(3-thienylmethyl)-, (3S,4S)-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C29 H30 N4 O4 S . 2 C2 H F3 O2
SR CA

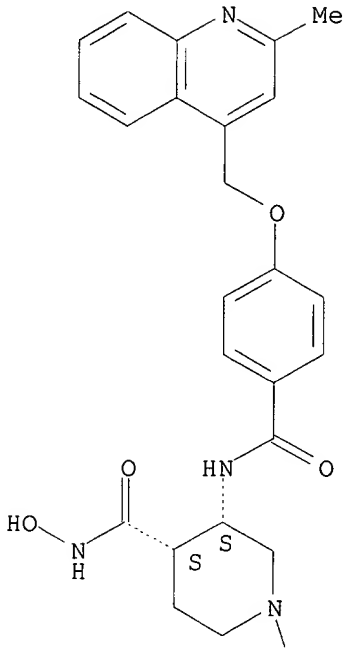
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

CM 1

CRN 362487-22-7
CMF C29 H30 N4 O4 S

Absolute stereochemistry.

PAGE 1-A



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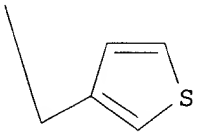
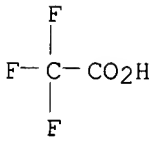


CM 2

CRN 76-05-1
CMF C2 H F3 O2



1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 135:257169

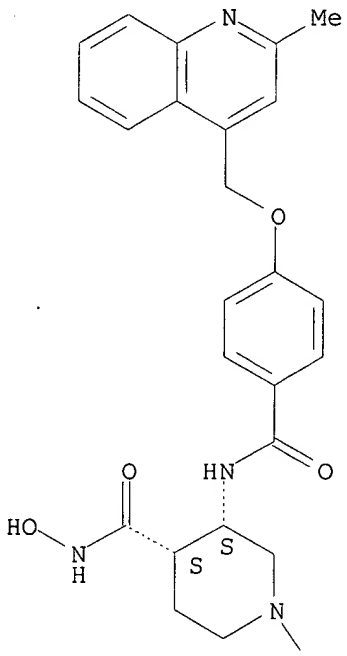
L20 ANSWER 750 OF 1197 REGISTRY COPYRIGHT 2003 ACS
RN **362486-45-1** REGISTRY
CN 4-Piperidinecarboxamide, N-hydroxy-1-(2-methylpropyl)-3-[[4-[(2-methyl-4-quinolinyl)methoxy]benzoyl]amino]-, (3S,4S)-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C28 H34 N4 O4 . 2 C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

CM 1

CRN 362486-44-0
CMF C28 H34 N4 O4

Absolute stereochemistry.

PAGE 1-A

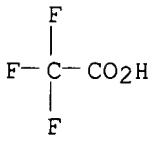


PAGE 2-A

Bu-i

CM 2

CRN 76-05-1
CMF C2 H F3 O2



1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 135:257169

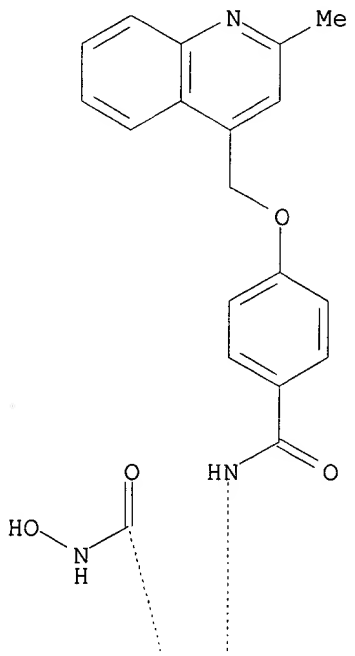
L20 ANSWER 800 OF 1197 REGISTRY COPYRIGHT 2003 ACS
RN **362485-91-4** REGISTRY
CN 3-Piperidinecarboxamide, N-hydroxy-4-[[4-[(2-methyl-4-quinolinyl)methoxy]benzoyl]amino]-1-(2-thiazolylmethyl)-, (3S,4R)-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C28 H29 N5 O4 S . 2 C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

CM 1

CRN 362485-90-3
CMF C28 H29 N5 O4 S

Absolute stereochemistry.

PAGE 1-A



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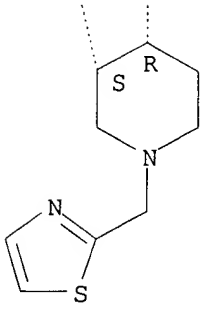
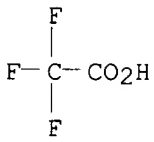


CM 2

CRN 76-05-1
CMF C2 H F3 O2



1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 135:257169

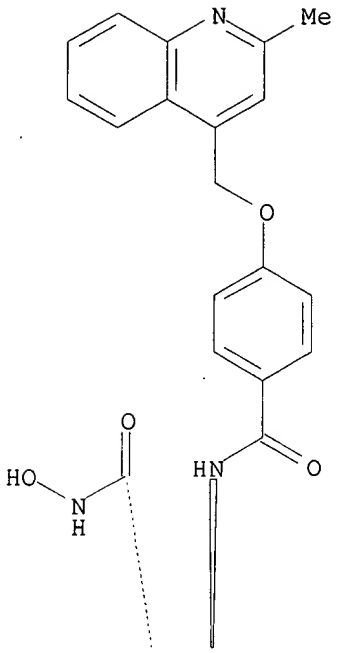
L20 ANSWER 850 OF 1197 REGISTRY COPYRIGHT 2003 ACS
RN **362485-41-4** REGISTRY
CN 1-Pyrrolidinecarboxylic acid, 3-[(hydroxyamino)carbonyl]-4-[[4-[(2-methyl-4-quinolinyl)methoxy]benzoyl]amino]-, 1,1-dimethylethyl ester, (3R,4S)-rel-, mono(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C28 H32 N4 O6 . C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

CM 1

CRN 362485-40-3
CMF C28 H32 N4 O6

Relative stereochemistry.

PAGE 1-A



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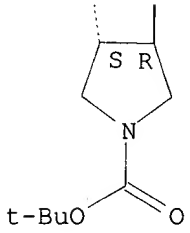
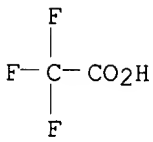


CM 2

CRN 76-05-1
CMF C2 H F3 O2



1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

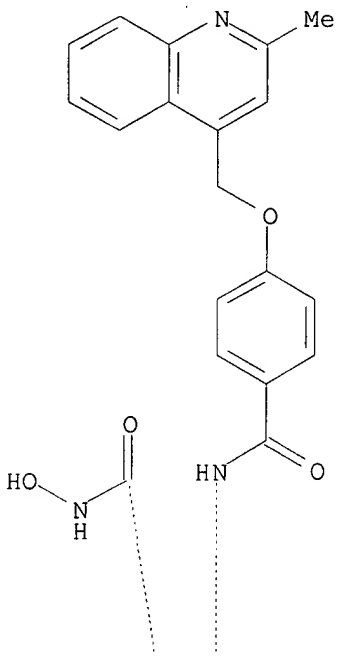
REFERENCE 1: 135:257169

L20 ANSWER 900 OF 1197 REGISTRY COPYRIGHT 2003 ACS
RN **362484-54-6** REGISTRY

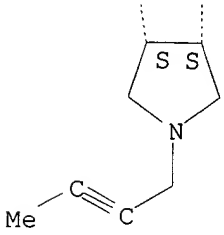
CN 3-Pyrrolidinecarboxamide, 1-(2-butynyl)-N-hydroxy-4-[[4-[(2-methyl-4-quinolinyl)methoxy]benzoyl]amino]-, (3S,4S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C27 H28 N4 O4
CI COM
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

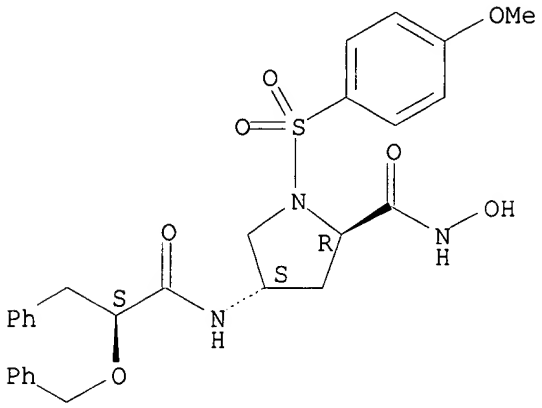
1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 135:257169

L20 ANSWER 950 OF 1197 REGISTRY COPYRIGHT 2003 ACS
RN **317860-44-9** REGISTRY
CN 2-Pyrrolidinecarboxamide, N-hydroxy-1-[(4-methoxyphenyl)sulfonyl]-4-[[(2S)-1-oxo-3-phenyl-2-(phenylmethoxy)propyl]amino]-, (2R,4S)- (9CI) (CA INDEX

NAME)
FS STEREOSEARCH
MF C28 H31 N3 O7 S
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



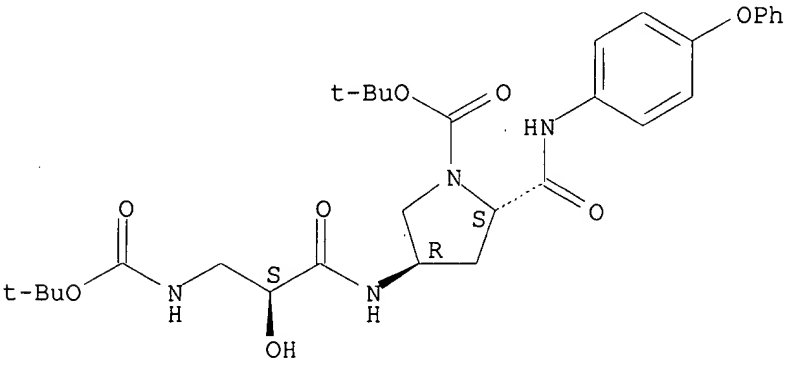
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 134:101151

L20 ANSWER 1000 OF 1197 REGISTRY COPYRIGHT 2003 ACS
RN **254883-01-7** REGISTRY
CN 1-Pyrrolidinecarboxylic acid, 4-[[(2S)-3-[[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-1-oxopropyl]amino]-2-[[(4-phenoxyphenyl)amino]carbonyl]-, 1,1-dimethylethyl ester, (2S,4R)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C30 H40 N4 O8
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.



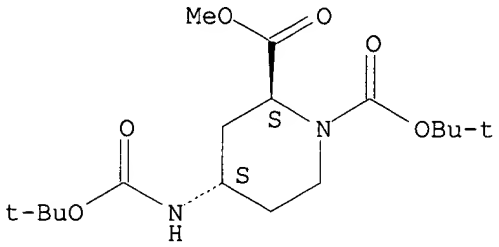
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 132:93658

L20 ANSWER 1050 OF 1197 REGISTRY COPYRIGHT 2003 ACS
RN **254882-10-5** REGISTRY
CN 1,2-Piperidinedicarboxylic acid, 4-[[(1,1-dimethylethoxy)carbonyl]amino]-, 1-(1,1-dimethylethyl) 2-methyl ester, (2S,4S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C17 H30 N2 O6
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.



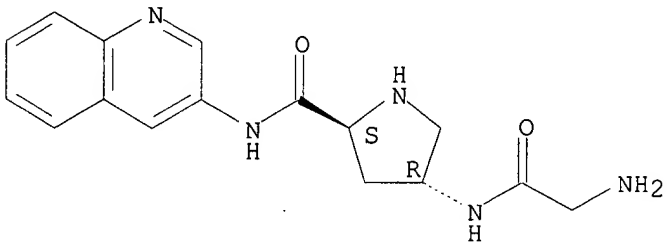
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 132:93658

L20 ANSWER 1100 OF 1197 REGISTRY COPYRIGHT 2003 ACS
RN **254881-17-9** REGISTRY
CN 2-Pyrrolidinecarboxamide, 4-[(aminoacetyl)amino]-N-3-quinolinyl-, trihydrochloride, (2S,4R)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C16 H19 N5 O2 . 3 Cl H
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.



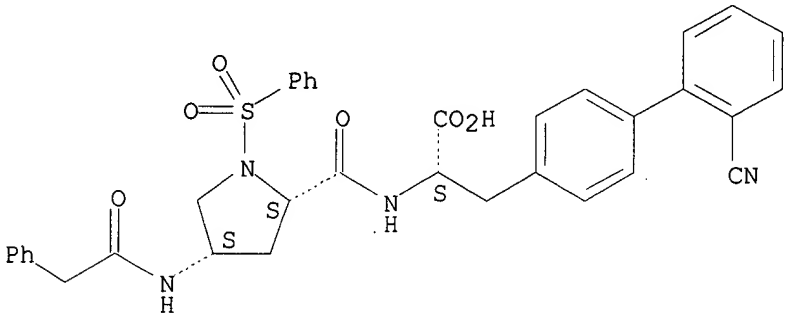
3 HCl

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 132:93658

L20 ANSWER 1150 OF 1197 REGISTRY COPYRIGHT 2003 ACS
RN **217325-51-4** REGISTRY
CN L-Alanine, (4S)-4-[(phenylacetyl)amino]-1-(phenylsulfonyl)-L-prolyl-3-(2'-cyano[1,1'-biphenyl]-4-yl)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C35 H32 N4 O6 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.



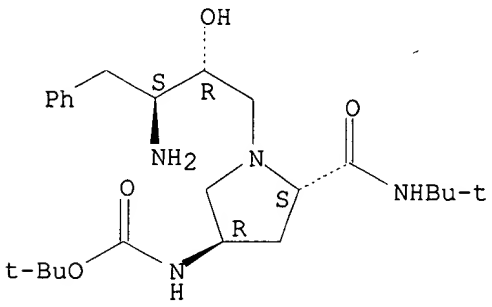
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 130:52736

L20 ANSWER 1197 OF 1197 REGISTRY COPYRIGHT 2003 ACS
RN **128019-81-8** REGISTRY
CN Carbamic acid, [1-(3-amino-2-hydroxy-4-phenylbutyl)-5-[[(1,1-dimethylethyl)amino]carbonyl]-3-pyrrolidinyl]-, 1,1-dimethylethyl ester, [3R-[1(2R*,3S*),3.alpha.,5.beta.]]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C24 H40 N4 O4
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1962 TO DATE)
1 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 113:41332

L12 ANSWER 1 OF 2 USPATFULL

DETD It has also been shown that IL-1 may affect the pathogenesis of atherosclerosis directly, by stimulating smooth muscle cell proliferation or, indirectly, through the action of **platelet** -derived growth factor (PDGF). See Jackson, R. L. and Ku, G., Interleukin-1.beta., its Role in the Pathogenesis of Atherosclerosis and Agent that Inhibit its Action, Current Drugs: Anti-atherosclerotic Agents, pp. B31-B42 (October 1991). In addition, Tenidap, an agent known to block IL-1 production, reduces the total level of serum cholesterol, serum LDL cholesterol and serum triglycerides in a mammal having an arthritic condition for which Tenidap is being administered. See U.S. Pat. No. 5,122,534 (Feb. 8, 1991). Thus agents which inhibit IL-1 action may also be useful in the prophylactic treatment of atherosclerosis.

IT 51685-51-9P, 2-Benzoylchromone 80575-55-9P, 2-(4-Methoxybenzoyl)chromone 167026-10-0P 167026-11-1P 167026-12-2P **167026-13-3P** 167026-14-4P 167026-15-5P 167026-16-6P 167026-17-7P, 5,7-Dichloro-4-(benzyloxy)-2-benzoylquinoline 167026-18-8P, 5,7-Dichloro-4-(benzyloxy)-2-acetylquinoline 167026-19-9P, 5,7-Dichloro-2-benzoyl-1,4-dihydroquinolin-4-one 167026-20-2P, 5,7-Dichloro-2-acetyl-1,4-dihydroquinolin-4-one 167026-26-8P 167026-27-9P 167026-28-0P
(intermediate; prepn. of benzenesulfonylimine derivs. as IL-1 inhibitors)

IT **167026-21-3P**, 5,7-Dichloro-2-benzoyl-4-(benzenesulfonylimino)-1,4-dihydroquinoline **167026-22-4P** 167026-23-5P, 2-Benzoyl-4-(benzenesulfonylimino)-4H-chromene 167026-25-7P, 2-(4-Hydroxybenzoyl)-4-(benzenesulfonylimino)-4H-chromene **167026-29-1P**, 5,7-Dichloro-2-(4-aminobenzoyl)-4-(benzenesulfonylimino)-1,4-dihydroquinoline **167026-30-4P**, 5,7-Dichloro-2-(2-aminobenzoyl)-4-(benzenesulfonylimino)-1,4-dihydroquinoline 167026-31-5P, 2-(4-Aminobenzoyl)-4-(benzenesulfonylimino)-4H-chromene 167026-32-6P, 5,7-Dichloro-2-benzoyl-4-(benzenesulfonylimino)-4H-chromene
(prepn. of benzenesulfonylimine derivs. as IL-1 inhibitors)

ACCESSION NUMBER: 97:101771 USPATFULL

TITLE: Benzenesulfonylimine derivatives as inhibitors of IL-1 action

INVENTOR(S): Harrison, Boyd L., Cincinnati, OH, United States
Ku, George, Burlington, MA, United States
Meikrantz, Scott B., Carson City, NV, United States
Dalton, Christopher R., Mundelein, IL, United States
Stemerick, David M., Fairfield, OH, United States

PATENT ASSIGNEE(S): Merrell Pharmaceuticals Inc., Cincinnati, OH, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5684017		19971104	
	WO 9514669		19950601	
APPLICATION INFO.:	US 1996-649663		19960806	(8)
	WO 1994-US12658		19941103	
			19960806	PCT 371 date
			19960806	PCT 102(e) date

RELATED APPLN. INFO.: Continuation of Ser. No. US 1993-159014, filed on 29 Nov 1993, now abandoned

DOCUMENT TYPE: Utility

FILE SEGMENT: Granted

PRIMARY EXAMINER: Morris, Patricia L.

LEGAL REPRESENTATIVE: Sayles, Michael J.

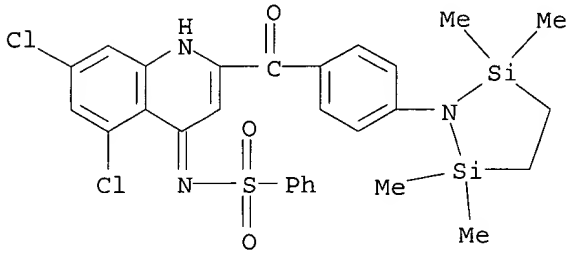
NUMBER OF CLAIMS: 7

EXEMPLARY CLAIM: 1

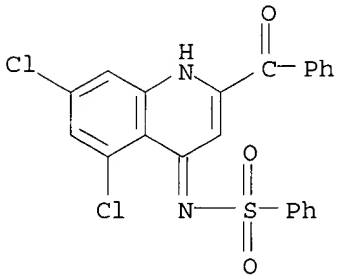
LINE COUNT: 990

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

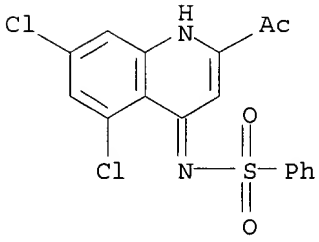
IT **167026-13-3P**
(intermediate; prepn. of benzenesulfonylimine derivs. as IL-1 inhibitors)
RN 167026-13-3 USPATFULL
CN Benzenesulfonamide, N-[5,7-dichloro-2-[4-(2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopent-1-yl)benzoyl]-4(1H)-quinolinylidene]- (9CI) (CA INDEX NAME)



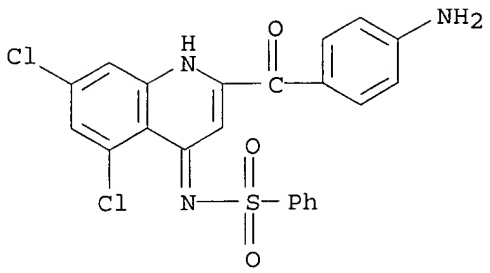
IT **167026-21-3P**, 5,7-Dichloro-2-benzoyl-4-(benzenesulfonylimino)-1,4-dihydroquinoline **167026-22-4P 167026-29-1P**, 5,7-Dichloro-2-(4-aminobenzoyl)-4-(benzenesulfonylimino)-1,4-dihydroquinoline **167026-30-4P**, 5,7-Dichloro-2-(2-aminobenzoyl)-4-(benzenesulfonylimino)-1,4-dihydroquinoline
(prepn. of benzenesulfonylimine derivs. as IL-1 inhibitors)
RN 167026-21-3 USPATFULL
CN Benzenesulfonamide, N-(2-benzoyl-5,7-dichloro-4(1H)-quinolinylidene)- (9CI) (CA INDEX NAME)



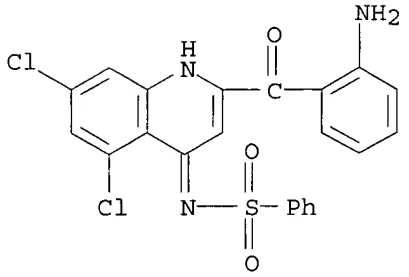
RN 167026-22-4 USPATFULL
CN Benzenesulfonamide, N-(2-acetyl-5,7-dichloro-4(1H)-quinolinylidene)- (9CI) (CA INDEX NAME)



RN 167026-29-1 USPATFULL
CN Benzenesulfonamide, N-[2-(4-aminobenzoyl)-5,7-dichloro-4(1H)-quinolinylidene]- (9CI) (CA INDEX NAME)



RN 167026-30-4 USPATFULL
CN Benzenesulfonamide, N-[2-(2-aminobenzoyl)-5,7-dichloro-4(1H)-quinolinylidene]- (9CI) (CA INDEX NAME)

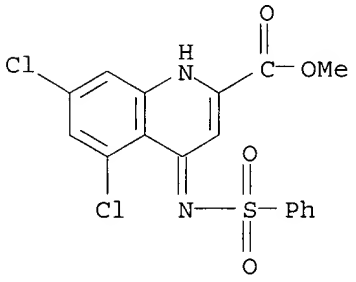


L12 ANSWER 2 OF 2 USPATFULL
DETD It has also been shown that IL-1 may affect the pathogenesis of atherosclerosis directly, by stimulating smooth muscle cell proliferation or, indirectly, through the action of **platelet**-derived growth factor (PDGF). See Jackson, R. L. and Ku, G., Interleukin-1.beta., its Role in the Pathogenesis of Atherosclerosis and Agents that Inhibit its Action, Current Drugs: Anti-atherosclerotic Agents, pp B31-B42 (October 1991). In addition, Tenidap, an agent known to block IL-1 production, reduces the total level of serum cholesterol, serum LDL cholesterol and serum triglycerides in a mammal having an arthritic condition for which Tenidap is being administered. See U.S. Pat. No. 5,122,534 (Feb. 8, 1991). Thus agents which inhibit IL-1 action may also be useful in the prophylactic treatment of atherosclerosis.
IT **144759-19-3P**, 5,7-Dichloro-4-(benzenesulfonylimino)-1,4-dihydroquinoline-2-carboxylic acid methyl ester
(prepn. of heterocyclic benzenesulfonylimine derivs. as inhibitors of IL-1)
IT **166981-72-2P**, 5,7-Dichloro-4-(benzenesulfonylimino)-1,4-dihydroquinoline-2-carboxylic acid ethyl ester **166981-73-3P**, 5,7-Dichloro-4-(benzenesulfonylimino)-1,4-dihydroquinoline-2-carboxylic acid butyl ester **166981-74-4P**, 5,7-Dichloro-4-(benzenesulfonylimino)-1,4-dihydroquinoline-2-carboxylic acid N-methylamide 166981-75-5P, 4-(Benzenesulfonylimino)-4H-chromene-2-carboxylic acid methyl ester 166981-76-6P, 4-(Benzenesulfonylimino)-4H-thiochromene-2-carboxylic acid methyl ester
(prepn. of heterocyclic benzenesulfonylimine derivs. as inhibitors of IL-1)
ACCESSION NUMBER: 97:83969 USPATFULL
TITLE: Heterocyclic benzenesulfonylimine derivatives as inhibitors of IL-1 action
INVENTOR(S): Ku, George, Burlington, MA, United States
Harrison, Boyd L., Cincinnati, OH, United States
Stemerick, David M., Fairfield, OH, United States
PATENT ASSIGNEE(S): Merrell Pharmaceuticals Inc., Cincinnati, OH, United

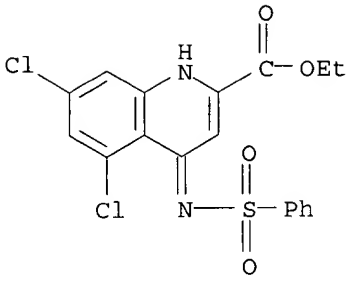
States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5668143		19970916	
	WO 9514670		19950601	
APPLICATION INFO.:	US 1996-648150		19960703	(8)
	WO 1994-US12575		19941103	
			19960703	PCT 371 date
			19960703	PCT 102(e) date

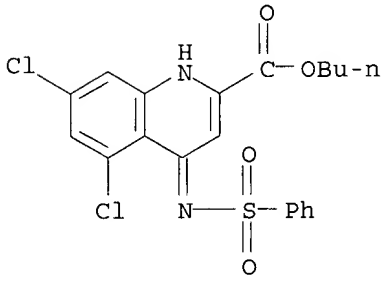
RELATED APPLN. INFO.: Continuation of Ser. No. US 1993-158661, filed on 29 Nov 1993, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Ivy, C. Warren
ASSISTANT EXAMINER: Covington, Raymond
LEGAL REPRESENTATIVE: Barney, Charlotte L.
NUMBER OF CLAIMS: 12
EXEMPLARY CLAIM: 1
LINE COUNT: 756
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **144759-19-3P**, 5,7-Dichloro-4-(benzenesulfonylimino)-1,4-dihydroquinoline-2-carboxylic acid methyl ester
(prepn. of heterocyclic benzenesulfonylimine derivs. as inhibitors of IL-1)
RN 144759-19-3 USPATFULL
CN 2-Quinolinecarboxylic acid, 5,7-dichloro-1,4-dihydro-4-[(phenylsulfonyl)imino]-, methyl ester (9CI) (CA INDEX NAME)



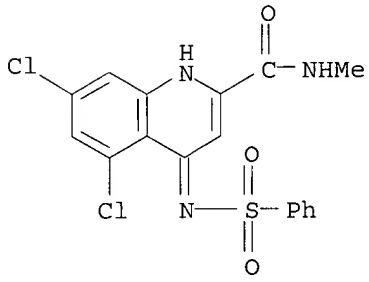
IT **166981-72-2P**, 5,7-Dichloro-4-(benzenesulfonylimino)-1,4-dihydroquinoline-2-carboxylic acid ethyl ester **166981-73-3P**, 5,7-Dichloro-4-(benzenesulfonylimino)-1,4-dihydroquinoline-2-carboxylic acid butyl ester **166981-74-4P**, 5,7-Dichloro-4-(benzenesulfonylimino)-1,4-dihydroquinoline-2-carboxylic acid N-methylamide
(prepn. of heterocyclic benzenesulfonylimine derivs. as inhibitors of IL-1)
RN 166981-72-2 USPATFULL
CN 2-Quinolinecarboxylic acid, 5,7-dichloro-1,4-dihydro-4-[(phenylsulfonyl)imino]-, ethyl ester (9CI) (CA INDEX NAME)



RN 166981-73-3 USPATFULL
CN 2-Quinolinecarboxylic acid, 5,7-dichloro-1,4-dihydro-4-[(phenylsulfonyl)imino]-, butyl ester (9CI) (CA INDEX NAME)



RN 166981-74-4 USPATFULL
CN 2-Quinolinecarboxamide, 5,7-dichloro-1,4-dihydro-N-methyl-4-[(phenylsulfonyl)imino]- (9CI) (CA INDEX NAME)



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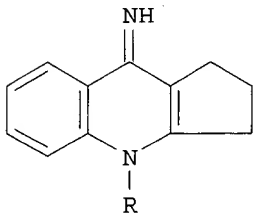
L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS
AN 2003:22624 CAPLUS
DN 138:66686
TI Compositions for inhibiting platelet activation and thrombosis
IN Flaumenhaft, Robert Charles
PA Beth Israel Deaconess Medical Center, USA
SO PCT Int. Appl., 100 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61B
CC 1-8 (Pharmacology)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003001968	A2	20030109	WO 2002-US19843	20020624

PI WO 2003001968 A2 20030109 WO 2002-US19843 20020624
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRAI US 2001-300932P P 20010626
OS MARPAT 138:66686
GI



I

AB The invention provides methods and compns. for reducing platelet activation, platelet aggregation and thrombosis. The invention further provides compns. and methods for treating or preventing diseases or disorders in which the pathol. of the disease or disorder involves one or more of platelet activation, platelet aggregation and thrombus formation. Example compds. are I (R = Pr, Bu, or pentyl).
ST platelet activation inhibitor compn; antithrombotic compn; quinoline imine deriv platelet activation inhibitor; heterocyclic compn platelet activation inhibitor
IT Platelet (blood)
(activation, inhibitors; compns. for inhibiting platelet activation and thrombosis)
IT Prosthetic materials and Prosthetics
(antithrombogenic; compns. for inhibiting platelet activation and thrombosis)
IT Anticoagulants
Platelet aggregation inhibitors
(compns. for inhibiting platelet activation and thrombosis)
IT Antibodies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(compns. for inhibiting platelet activation and thrombosis)

IT Integrins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.alpha.IIb.beta.3, inhibitors; compns. for inhibiting platelet activation and thrombosis)

IT 66-71-7, 1,10-Phenanthroline 26303-23-1 36725-41-4 54258-41-2, 1,10-Phenanthrolin-5-amine 83568-05-2 111789-90-3 312926-53-7 317335-73-2 352544-23-1 **481686-99-1** 481687-00-7 481687-01-8 481687-02-9 481687-03-0 481687-04-1 481687-05-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. for inhibiting platelet activation and thrombosis)

IT 50-78-2, Aspirin 55142-85-3, Ticlopidine 113665-84-2, Clopidogrel 143653-53-6, Abciximab 144494-65-5, Tirofiban 188627-80-7, Eptifibatide
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. for inhibiting platelet activation and thrombosis)

IT 9025-82-5, Phosphodiesterase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; compns. for inhibiting platelet activation and thrombosis)

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L6 ANSWER 4 OF 4 USPATFULL

AB The present invention makes available methods and reagents for inhibiting aberrant growth states resulting from hedgehog gain-of-function, ptc loss-of-function or smoothened gain-of-function comprising contacting the cell with a hedgehog antagonist, such as a small molecule, in a sufficient amount to aberrant growth state, e.g., to agonize a normal ptc pathway or antagonize smoothened or hedgehog activity.

CLM What is claimed is:

1. A pharmaceutical formulation comprising an aqueous solution of a pharmaceutically acceptable salt of a compound represented in the general formula (I): ##STR34## wherein, as valence and stability permit, R.sub.1 and R.sub.4, independently for each occurrence, represent H, lower alkyl, --(CH.sub.2).sub.naryl, or --(CH.sub.2).sub.nheteroaryl; L, independently for each occurrence, is absent or represents --(CH.sub.2).sub.n--, -alkenyl-, -alkynyl-, --(CH.sub.2).sub.nalkenyl-, --(CH.sub.2).sub.nalkynyl-, --(CH.sub.2).sub.nO(CH.sub.2).sub.p--, --(CH.sub.2).sub.nNR.sub.8(CH.sub.2).sub.p--, --(CH.sub.2).sub.nS(CH.sub.2).sub.p--, --(CH.sub.2).sub.nalkenyl(CH.sub.2).sub.p--, --(CH.sub.2).sub.nalkynyl(CH.sub.2).sub.p--, --O(CH.sub.2).sub.n--, --NR.sub.8(CH.sub.2).sub.n--, or --S(CH.sub.2).sub.n--; X and D, independently, are selected from --N(R.sub.8)--, --O--, --S--, --(R.sub.8)N--N(R.sub.8)--, --ON(R.sub.8)--, and a direct bond; Y and Z, independently, are selected from O and S; E represents NR.sub.5, wherein R.sub.5 represents LR.sub.8 or an ammonium salt thereof; R.sub.8, independently for each occurrence, represents H, lower alkyl, --(CH.sub.2)naryl, or --(CH.sub.2).sub.nheteroaryl, or two R.sub.8 taken together may form a 4- to 8-membered ring; p represents, independently for each occurrence, an integer from 0 to 3; n, individually for each occurrence, represents an integer from 0 to 5; and q and r represent, independently for each occurrence, an integer from 0 to 2.

2. The formulation of claim 1, wherein Y and Z each represent O.

3. The formulation of claim 1, wherein the sum of q and r is less than 4.

4. The formulation of claim 1, wherein D represents an aralkyl- or heteroaralkyl-substituted amine.

5. The formulation of claim 1, wherein R.sub.1 represents a branched alkyl, a cycloalkyl, or a cycloalkylalkyl.

6. The formulation of claim 1, wherein L attached to R.sub.1 represents O, S, or NR.sub.8.

8. The formulation of claim 1, wherein X is included in a ring.

9. The formulation of claim 1, wherein XLR.sub.4 includes a cyclic amine.

10. The formulation of claim 1, wherein the salt is a chloride, bromide, iodide, succinate, tartrate, lactate, mesylate, or maleate salt.

11. The formulation of claim 1, wherein the solution includes a dissolved physiologically acceptable salt.

12. The formulation of claim 11, wherein the physiologically salt is sodium acetate.

13. The formulation of claim 1, wherein the aqueous solution further

includes a solute selected from dextrose, lactose, mannitol, or another polyhydroxylated compound.

14. The formulation of claim 1, wherein the aqueous solution has an osmolarity between 200 and 400 mOsm.

15. The formulation of claim 1, wherein the solution has a pH in the range of 3 to 6.

16. The formulation of claim 1, wherein the formulation is suitable for topical administration.

17. A pharmaceutical formulation comprising an aqueous solution of a pharmaceutically acceptable salt of a compound represented in the general formula (II): ##STR35## wherein, as valence and stability permit, R.sub.1 R.sub.2, R.sub.3, and R.sub.4, independently for each occurrence, represent H, lower alkyl, --(CH.sub.2).sub.naryl, or --(CH.sub.2).sub.nheteroaryl; L, independently for each occurrence, is absent or represents --(CH.sub.2).sub.n--, -alkenyl-, -alkynyl-, --(CH.sub.2).sub.nalkenyl-, --(CH.sub.2).sub.nalkynyl-, --(CH.sub.2).sub.nO(cH.sub.2).sub.p--, --(CH.sub.2).sub.nNR.sub.8(CH.sub.2).sub.p--, --(CH.sub.2).sub.nS(CH.sub.2).sub.p--, --(CH.sub.2).sub.nalkenyl(CH.sub.2).sub.p--, --(CH.sub.2).sub.nalkynyl(CH.sub.2).sub.p--, --O(CH.sub.2).sub.n--, --NR.sub.s(CH.sub.2).sub.n--, or --S(CH.sub.2).sub.n--; X is selected, independently, from --N(R.sub.8)--, --O--, --S--, --(R.sub.8)N--N(R.sub.8)--, --ON(R.sub.8)--, and a direct bond; Y and Z, independently, are selected from O and S; R.sub.8, independently for each occurrence, represents H, lower alkyl, --(CH.sub.2).sub.naryl, or --(CH.sub.2).sub.nheteroaryl, or two R.sub.8 taken together may form a 4- to 8-membered ring; M is absent or represents L, --SO.sub.2L--, or --(C.dbd.O)L--; p represents, independently for each occurrence, an integer from 0 to 3; n, individually for each occurrence, represents an integer from 0 to 5; and q, r, and s represent, independently for each occurrence, an integer from 0 to 2.

18. The formulation of claim 17, wherein Y and Z each represent O.

19. The formulation of claim 17, wherein the sum of q, r, and s is less than 4.

20. The formulation of claim 17, wherein at least one of R.sub.1, R.sub.2, and R.sub.3 includes an aryl group.

21. The formulation of claim 17, wherein XLR.sub.4 includes a cyclic diamine.

22. The formulation of claim 17, wherein X is included in a diazacarbocycle.

23. The formulation of claim 17, wherein R.sub.1 represents a branched alkyl, a cycloalkyl, or a cycloalkylalkyl.

24. The formulation of claim 17, wherein L attached to R.sub.1 represents O, S, or NR.sub.8.

25. The formulation of claim 17, wherein the salt is a chloride, bromide, iodide, succinate, tartrate, lactate, mesylate, or maleate salt.

26. The formulation of claim 17, wherein the solution includes a dissolved physiologically acceptable salt.

27. The formulation of claim 26, wherein physiologically the salt is

sodium acetate.

28. The formulation of claim 17, wherein the aqueous solution further includes a solute selected from dextrose, lactose, mannitol, or another polyhydroxylated compound.

29. The formulation of claim 17, wherein the aqueous solution has an osmolarity between 200 and 400 mOsm.

30. The formulation of claim 17, wherein the solution has a pH in the range of 3 to 6.

31. The formulation of claim 17, wherein the formulation is suitable for topical administration.

32. A method for inhibiting activation of a hedgehog pathway in a cell, comprising contacting the cell with the formulation of claim 1.

33. A method for inhibiting activation of a hedgehog pathway in a cell, comprising contacting the cell with the formulation of claim 17.

34. A method for treating or preventing basal cell carcinoma, comprising administering the formulation of claim 1 to a patient in an amount sufficient to inhibit progression of basal cell carcinoma.

35. A method for treating or preventing basal cell carcinoma, comprising administering the formulation of claim 17 to a patient in an amount sufficient to inhibit progression of basal cell carcinoma.

36. A pharmaceutical formulation comprising an aqueous solution of a pharmaceutically acceptable salt of a compound represented in the general formula (III): ##STR36## wherein, as valence and stability permit, R.sub.1, R.sub.2, R.sub.3, and R.sub.4, independently for each occurrence, represent H, lower alkyl, --(CH.sub.2).sub.naryl, or --(CH.sub.2).sub.nheteroaryl; L, independently for each occurrence, is absent or represents --(CH.sub.2).sub.n--, -alkenyl-, -alkynyl-, --(CH.sub.2).sub.nalkenyl--, --(CH.sub.2).sub.nalkynyl-, --(CH.sub.2).sub.nO(CH.sub.2).sub.p--, --(CH.sub.2).sub.nNR.sub.8(CH.sub.2).sub.p--, --(CH.sub.2).sub.nS(CH.sub.2).sub.p--, --(CH.sub.2).sub.nalkenyl(CH.sub.2).sub.p--, --(CH.sub.2).sub.nalkynyl(CH.sub.2).sub.p--, --O(CH.sub.2).sub.n--, --NR.sub.8(CH.sub.2).sub.n--, or --S(CH.sub.2).sub.n--; X is selected from --N(R.sub.8)--, --O--, --S--, --(R.sub.8)N--N(R.sub.8)--, --ON(R.sub.8)--, and a direct bond; Y and Z, independently, are selected from O and S; R.sub.8, independently for each occurrence, represents H, lower alkyl, --(CH.sub.2).sub.naryl, or --(CH.sub.2)nheteroaryl, or two R.sub.8 taken together may form a 4- to 8-membered ring; M is absent or represents L, --SO.sub.2L--, or --(C.dbd.O)L--; p represents, independently for each occurrence, an integer from 0 to 3; n, individually for each occurrence, represents an integer from 0 to 5; and q and r represent, independently for each occurrence, an integer from 0 to 2.

37. The formulation of claim 36, wherein the sum of q and r is less than 4.

38. The formulation of claim 36, wherein R.sub.1 represents a branched alkyl, a cycloalkyl, or a cycloalkylalkyl.

39. The formulation of claim 36, wherein XLR.sub.4 includes a cyclic amine.

40. The formulation of claim 36, wherein the salt is a chloride, bromide, iodide, succinate, tartrate, lactate, mesylate, or maleate

salt.

41. The formulation of claim 36, wherein the solution includes a dissolved physiologically acceptable salt.

42. The formulation of claim 41, wherein physiologically the salt is sodium acetate.

43. The formulation of claim 36, wherein the aqueous solution further includes a solute selected from dextrose, lactose, mannitol, or another polyhydroxylated compound.

44. The formulation of claim 36, wherein the aqueous solution has an osmolarity between 200 and 400 mOsm.

45. The formulation of claim 36, wherein the solution has a pH in the range of 3 to 6.

46. The formulation of claim 36, wherein the formulation is suitable for topical administration.

47. A pharmaceutical formulation comprising an aqueous solution of a pharmaceutically acceptable salt of a compound represented in the general formula (IV): ##STR37## wherein, as valence and stability permit, R.sub.1, R.sub.2, R.sub.3, and R.sub.4, independently for each occurrence, represent H, lower alkyl, --(CH.sub.2)naryl, or --(CH.sub.2).sub.nheteroaryl; L, independently for each occurrence, is absent or represents --(CH.sub.2).sub.n--, -alkenyl-, -alkynyl-, --(CH.sub.2).sub.nalkenyl-, --(CH.sub.2)nalkynyl-, --(CH.sub.2).sub.nO(CH.sub.2).sub.p--, --(CH.sub.2).sub.nNR.sub.8(CH.sub.2).sub.p--, --(CH.sub.2).sub.nS(CH.sub.2).sub.p--, --(CH.sub.2).sub.nalkenyl(CH.sub.2).sub.p--, --(CH.sub.2).sub.nalkynyl(CH.sub.2).sub.p--, --O(CH.sub.2).sub.n--, --NR.sub.8(CH.sub.2).sub.n--, or --S(CH.sub.2).sub.n--; X is selected, independently, from --N(R.sub.8)--, --O--, --S--, --(R.sub.8)N--N(R.sub.8)--, --ON(R.sub.8)--, and a direct bond; R.sub.8, independently for each occurrence, represents H, lower alkyl, --(CH.sub.2).sub.naryl, or --(CH.sub.2).sub.nheteroaryl, or two R.sub.8 taken together may form a 4- to 8-membered ring; M is absent or represents L, --SO.sub.2L--, or --(C.dbd.O)L--; p represents, independently for each occurrence, an integer from 0 to 3; and n, individually for each occurrence, represents an integer from 0 to 5.

48. The formulation of claim 47, wherein R.sub.1 represents a branched alkyl, a cycloalkyl, or a cycloalkylalkyl.

49. The formulation of claim 47, wherein at least one of R.sub.1, R.sub.2, and R.sub.3 includes an aryl group.

50. The formulation of claim 47, wherein XLR.sub.4 includes a cyclic amine.

51. The formulation of claim 47, wherein X is part of a diazacarbocycle.

52. The formulation of claim 47, wherein the salt is a chloride, bromide, iodide, succinate, tartrate, lactate, mesylate, or maleate salt.

53. The formulation of claim 47, wherein the solution includes a dissolved physiologically acceptable salt.

54. The formulation of claim 53, wherein physiologically the salt is sodium acetate.

55. The formulation of claim 47, wherein the aqueous solution further includes a solute selected from dextrose, lactose, mannitol, or another polyhydroxylated compound.

56. The formulation of claim 47, wherein the aqueous solution has an osmolarity between 200 and 400 mOsm.

57. The formulation of claim 47, wherein the solution has a pH in the range of 3 to 6.

58. The formulation of claim 47, wherein the formulation is suitable for topical administration.

59. A method for inhibiting activation of a hedgehog pathway in a cell, comprising contacting the cell with the formulation of claim 36.

60. A method for inhibiting activation of a hedgehog pathway in a cell, comprising contacting the cell with the formulation of claim 47.

61. A method for treating or preventing basal cell carcinoma, comprising administering the formulation of claim 36 to a patient in an amount sufficient to inhibit progression of basal cell carcinoma.

62. A method for treating or preventing basal cell carcinoma, comprising administering the formulation of claim 47 to a patient in an amount sufficient to inhibit progression of basal cell carcinoma.

63. A pharmaceutical formulation comprising an aqueous solution of a pharmaceutically acceptable salt of a compound represented by the general formula (V): ##STR38## wherein, as valence and stability permit, Y is O or S; Z' is SO.sub.2, --(C.dbd.S)--, or--(C.dbd.O)--; p represents, independently for each occurrence, an integer from 0 to 3; n, individually for each occurrence, represents an integer from 0 to 5; q and r represent, independently for each occurrence, an integer fLrom C to 2; V is absent or represents O, S, or NR.sub.8; G is absent or represents --C(.dbd.O)-- or --SO.sub.2--; J, independently for each occurrence, represents H or substituted or unsubstituted lower alkyl or alkylene attached to NC(.dbd.Y), such that both occurrences of N adjacent to J are linked through at least one occurrence of J, and R.sub.9, independently for each occurrence, is absent or represents H or lower alkyl, or two occurrences of J or one occurrence of J taken together with one occurrence of R.sub.9, forms a ring of from 5 to 7 members, which ring includes one or both occurrences of N; R.sub.5 represents substituted or unsubstituted alkyl (branched or unbranched), alkenyl (branched or unbranched), alkynyl (branched or unbranched), cycloalkyl, or cycloalkylalkyl; R.sub.6 represents substituted or unsubstituted aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl, heterocyclylalkyl, cycloalkyl, or cycloalkylalkyl, including polycyclic groups; and R.sub.7 represents substituted or unsubstituted aryl, aralkyl, heteroaryl, or heteroaralkyl.

64. The formulation of claim 63, wherein Y and Z are O.

65. The formulation of claim 63, wherein the sum of q and r is less than 4.

66. The formulation of claim 63, wherein at least one occurrence of J is part of a heterocyclic ring having from 5 to 8 members.

67. The formulation of claim 63, wherein R.sub.5 represents a branched alkyl, cycloalkyl, or cycloalkylalkyl.

68. The formulation of claim 63, wherein R.sub.6 includes at least one heterocyclic ring.

69. The formulation of claim 63, wherein R.sub.7 represents a phenyl alkyl.

70. The formulation of claim 63, wherein the salt is a chloride, bromide, iodide, succinate, tartrate, lactate, mesylate, or maleate salt.

71. The formulation of claim 63, wherein the solution includes a dissolved physiologically acceptable salt.

72. The formulation of claim 71, wherein physiologically the salt is sodium acetate.

73. The formulation of claim 63, wherein the aqueous solution further includes a solute selected from dextrose, lactose, mannitol, or another polyhydroxylated compound.

74. The formulation of claim 63, wherein the aqueous solution has an osmolarity between 200 and 400 mOsm.

75. The formulation of claim 63, wherein the solution has a pH in the range of 3 to 6.

76. The formulation of claim 63, wherein the formulation is suitable for topical administration.

77. A method for inhibiting activation of a hedgehog pathway in a cell, comprising contacting the cell with the formulation of claim 63.

78. A method for treating or preventing basal cell carcinoma, comprising administering the formulation of claim 63 to a patient in an amount sufficient to inhibit progression of basal cell carcinoma.

79. A pharmaceutical formulation comprising an aqueous solution of a pharmaceutically acceptable salt of a compound represented by the general formula (VI): ##STR39## wherein, as valence and stability permit, Y is O or S; Z' is SO.sub.2, --(C.dbd.S)--, or --(C.dbd.O)--; p represents, independently for each occurrence, an integer from 0 to 3; n, individually for each occurrence, represents an integer from 0 to 5; V is absent or represents O, S, or NR.sub.8; G is absent or represents--C(.dbd.O)-- or --SO.sub.2--; J, independently for each occurrence, represents H or substituted or unsubstituted lower alkyl or alkylene attached to NC(.dbd.Y), such that both occurrences of N adjacent to J are linked through at least one occurrence of J, and R.sub.9, independently for each occurrence, is absent or represents H or lower alkyl, or two occurrences of J or one occurrence of J taken together with one occurrence of R.sub.9, forms a ring of from 5 to 7 members, which ring includes one or both occurrences of N; R.sub.5 represents substituted or unsubstituted alkyl (branched or unbranched), alkenyl (branched or unbranched), alkynyl (branched or unbranched), cycloalkyl, or cycloalkylalkyl; R.sub.6 represents substituted or unsubstituted aryl, aralkyl, heteroaryl, heteroaralkyl, heterocyclyl, heterocyclylalkyl, cycloalkyl, or cycloalkylalkyl, including polycyclic groups; and R.sub.7 represents substituted or unsubstituted aryl, aralkyl, heteroaryl, or heteroaralkyl.

80. The preparation of claim 79, wherein Y and Z are O.

81. The preparation of claim 79, wherein at least one occurrence of J is part of a heterocyclic ring having from 5 to 8 members.

82. The preparation of claim 79, wherein R.sub.5 represents a branched alkyl, cycloalkyl, or cycloalkylalkyl.

83. The preparation of claim 79, wherein R.sub.6 includes at least one heterocyclic ring.

84. The preparation of claim 79, wherein R.sub.7 represents a phenyl alkyl.

85. The formulation of claim 79, wherein the salt is a chloride, bromide, iodide, succinate, tartrate, lactate, mesylate, or maleate salt.

86. The formulation of claim 79, wherein the solution includes a dissolved physiologically acceptable salt.

87. The formulation of claim 86, wherein physiologically the salt is sodium acetate.

88. The formulation of claim 79, wherein the aqueous solution further includes a solute selected from dextrose, lactose, mannitol, or another polyhydroxylated compound.

89. The formulation of claim 79, wherein the aqueous solution has an osmolarity between 200 and 400 mOsm.

90. The formulation of claim 79, wherein the solution has a pH in the range of 3 to 6.

91. The formulation of claim 79, wherein the formulation is suitable for topical administration.

92. A method for inhibiting activation of a hedgehop pathway in a cell, comprising contacting the cell with the formulation of claim 79.

93. A method for treating or preventing basal cell carcinoma, comprising administering the formulation of claim 79 to a patient in an amount sufficient to inhibit progression of basal cell carcinoma.

IT 77-59-8, Tomatidine 78-41-1, Triparanol 366-93-8, AY9944 469-59-0, Jervine 4449-51-8, Cyclopamine 330796-27-5 **334998-27-5**
(hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

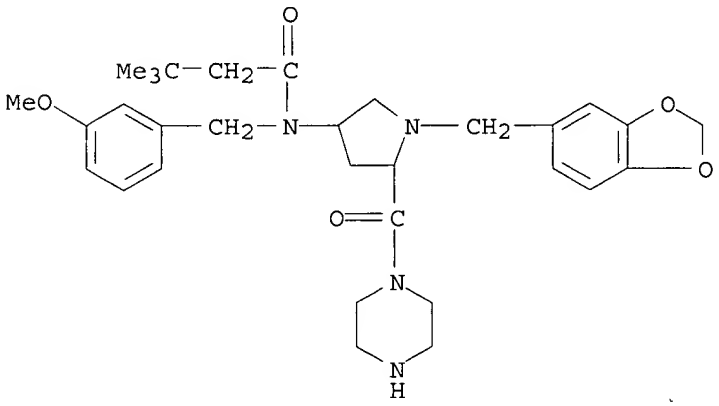
ACCESSION NUMBER: 2002:295175 USPATFULL
TITLE: Mediators of hedgehog signaling pathways, compositions and uses related thereto
INVENTOR(S): Baxter, Anthony David, Hertfordshire, UNITED KINGDOM
Boyd, Edward Andrew, Oxfordshire, UNITED KINGDOM
Guicherit, Oivin M., Belmont, MA, UNITED STATES
Price, Stephen, Buckinghamshire, UNITED KINGDOM
Rubin, Lee L., Wellesley, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002165221	A1	20021107
APPLICATION INFO.:	US 2001-977096	A1	20011012 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-240536P	20001013 (60)
	US 2000-240564P	20001013 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: ROPES & GRAY, ONE INTERNATIONAL PLACE, BOSTON, MA,

02110-2624
NUMBER OF CLAIMS: 92
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 58 Drawing Page(s)
LINE COUNT: 5140
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **334998-27-5**
(hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)
RN 334998-27-5 USPATFULL
CN Butanamide, N-[1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl- (9CI) (CA INDEX NAME)



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L6 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2003 ACS
AN 2001:283777 CAPLUS
DN 134:311102
TI Preparation and formulation of heterocycles as mediators of hedgehog signaling pathways for pharmaceutical and cosmetic uses
IN Baxter, Anthony David; Boyd, Edward Andrew; Guicherit, Oivin M.; Price, Stephen; Rubin, Lee
PA Curis, Inc., USA
SO PCT Int. Appl., 219 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-00
CC 27-10 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 62, 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001026644	A2	20010419	WO 2000-US28579	20001013
	WO 2001026644	A3	20020418		
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	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	EP 1227805	A2	20020807	EP 2000-978225	20001013
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
	JP 2003511411	T2	20030325	JP 2001-529434	20001013
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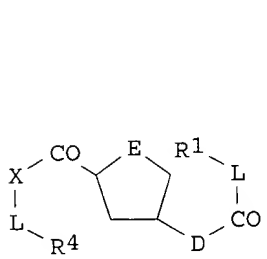
	US 2000-196543P	P	20000411		
	WO 2000-US28579	W	20001013		

OS MARPAT 134:311102
GI



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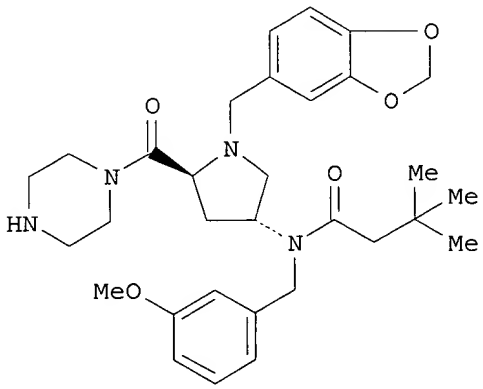


II

AB Heterocycles, such as I [E = O, S, NR; D, X = NR2, O, S, bond, etc.; L = linking group, such as alkylene, alkenylene, alkynylene; XL = piperazin-1,4-diyl, etc.; R, R1, R2 = H, alkyl, acyl, arylalkyl, heteroarylalkyl, etc.], were prepd. for pharmaceutical and cosmetic use. Thus, pyrrolidine II was prepd. via a multistep synthetic sequence which started with trans-4-hydroxy-L-proline, 3-methoxybenzaldehyde, piperonal,

tert-butylacetyl chloride, and N-(tert-butoxycarbonyl)piperazine. The prepd. pyrrolidines were tested for agonist activity for inhibiting aberrant growth states resulting from hedgehog gain-of-function, ptc loss-of-function or smoothened gain-of-function comprising contacting the cell with a hedgehog antagonist, such as a small mol., in a sufficient amt. to aberrant growth state, e.g., to agonize a normal ptc pathway or antagonize smoothened or hedgehog activity.

ST pyrrolidine prepn hedgehog signaling pathway mediator; cosmetic pyrrolidine prepn hedgehog signaling pathway mediator; basal cell carcinoma preventative pyrrolidine prepn; spermatogenesis regulator pyrrolidine prepn; hematopoiesis regulator pyrrolidine prepn

IT Skin, neoplasm
(basal cell carcinoma, preventative; prepn. and formulation of pyrrolidines for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

IT Cosmetics
(prepn. and formulation of pyrrolidines for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

IT Hematopoiesis
Spermatogenesis
(regulators; prepn. and formulation of pyrrolidines for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

IT Hedgehog protein
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(sonic; prepn. and formulation of pyrrolidines for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

IT **334999-41-6P 334999-57-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. and formulation of pyrrolidines for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

IT 334998-24-2P 334998-25-3P 334998-26-4P **334998-27-5P**
334998-28-6P 334998-29-7P 334998-30-0P 334998-31-1P 334998-32-2P
334998-33-3P 334998-34-4P 334998-35-5P **334998-36-6P**
334998-37-7P 334998-38-8P 334998-39-9P 334998-40-2P
334998-41-3P 334998-42-4P 334998-43-5P 334998-44-6P 334998-45-7P
334998-46-8P 334998-47-9P 334998-48-0P 334998-49-1P 334998-50-4P
334998-51-5P 334998-52-6P 334998-53-7P 334998-54-8P 334998-55-9P
334998-56-0P 334998-57-1P 334998-58-2P 334998-59-3P 334998-60-6P
334998-61-7P 334998-62-8P 334998-63-9P 334998-64-0P 334998-65-1P
334998-66-2P 334998-67-3P 334998-68-4P 334998-69-5P 334998-70-8P
334998-71-9P 334998-72-0P 334998-73-1P 334998-74-2P 334998-75-3P
334998-76-4P 334998-77-5P 334998-78-6P 334998-79-7P 334998-80-0P
334998-81-1P 334998-82-2P 334998-83-3P 334998-84-4P 334998-85-5P
334998-86-6P 334998-87-7P 334998-88-8P 334998-89-9P 334998-90-2P
334998-91-3P 334998-92-4P 334998-93-5P 334998-94-6P 334998-95-7P
334998-96-8P 334998-97-9P 334998-98-0P 334998-99-1P
334999-00-7P 334999-03-0P 334999-05-2P 334999-07-4P
334999-09-6P 334999-11-0P 334999-13-2P 334999-15-4P 334999-17-6P
334999-19-8P 334999-21-2P 334999-24-5P 334999-94-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and formulation of pyrrolidines for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

IT 51-35-4 591-31-1 623-05-2 7065-46-5 7693-46-1 57260-71-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. and formulation of pyrrolidines for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

IT 623-05-2DP, polymer bound 40216-83-9P 74844-91-0P 84520-67-2P

84520-68-3P 121147-97-5P 121148-01-4P 334999-29-0P 334999-32-5P
334999-33-6P 334999-34-7P 334999-35-8P 334999-36-9P 334999-37-0P
334999-38-1P 334999-39-2P 334999-43-8P 334999-45-0P 334999-47-2P
334999-48-3P 334999-51-8P 334999-53-0P 334999-55-2P 334999-60-9DP,
polymer bound
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and formulation of pyrrolidines for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

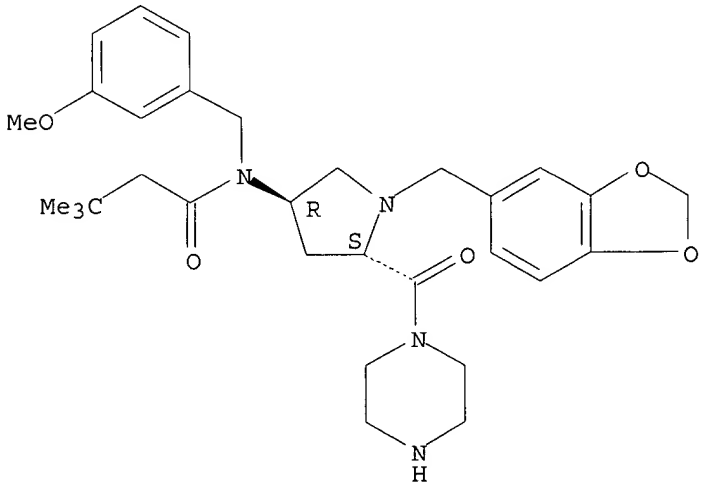
IT **334999-41-6P 334999-57-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. and formulation of pyrrolidines for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

RN 334999-41-6 CAPLUS
CN Butanamide, N-[(3R,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl-, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

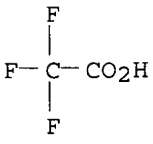
CRN 334998-37-7
CMF C31 H42 N4 O5

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2



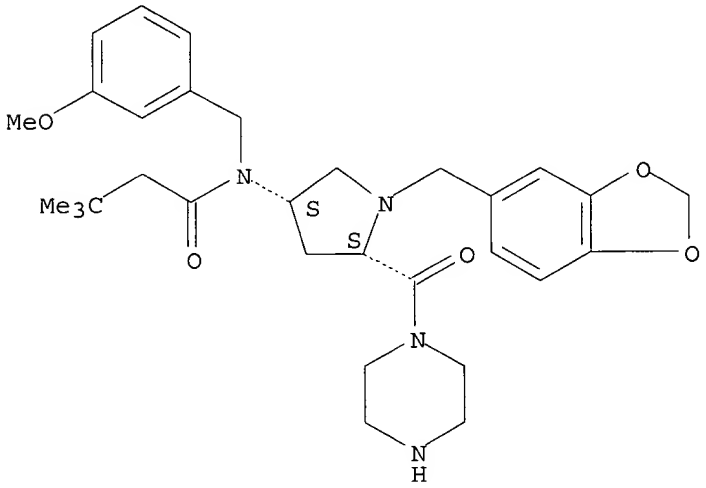
RN 334999-57-4 CAPLUS

CN Butanamide, N-[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl-, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

CRN 334998-36-6
CMF C31 H42 N4 O5

Absolute stereochemistry.



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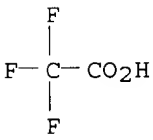
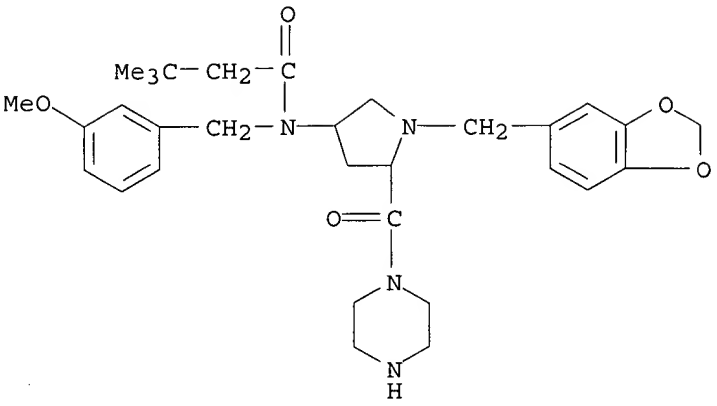
CRN 76-05-1
CMF C2 H F3 O2



IT **334998-27-5P 334998-36-6P 334998-37-7P**
334999-00-7P 334999-03-0P 334999-19-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and formulation of pyrrolidines for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

RN 334998-27-5 CAPLUS
CN Butanamide, N-[1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl- (9CI) (CA INDEX NAME)



RN 334998-36-6 CAPLUS
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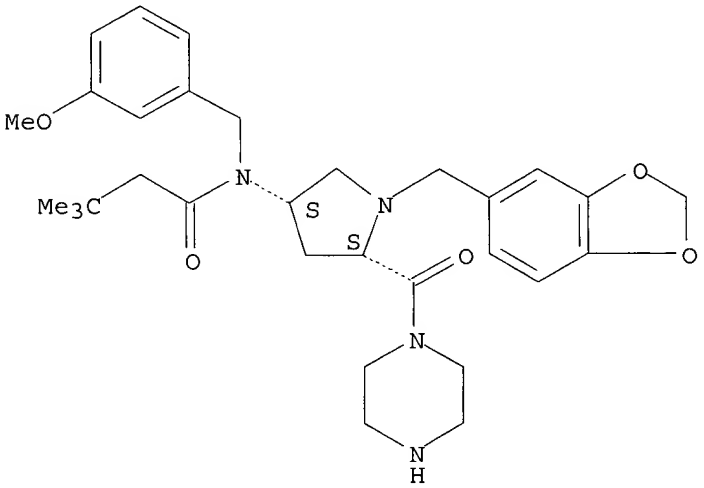
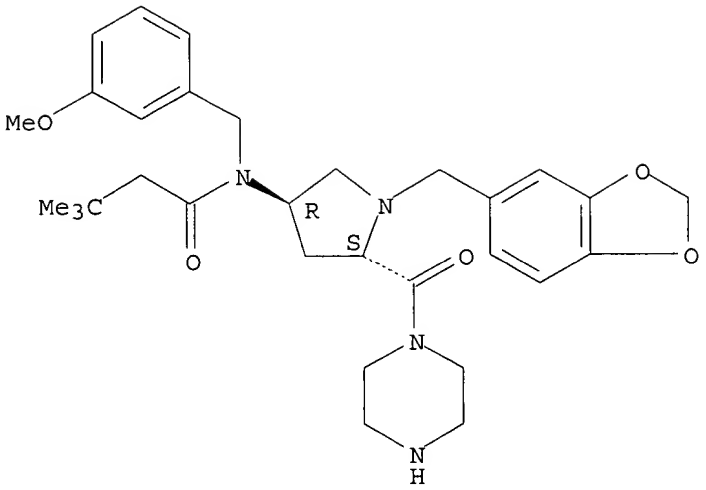
Absolute stereochemistry.



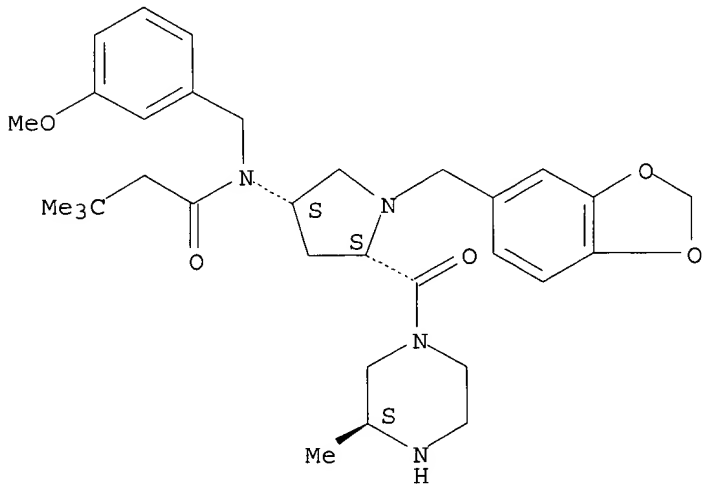
RN 334998-37-7 CAPLUS
CN Butanamide, N-[(3R,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



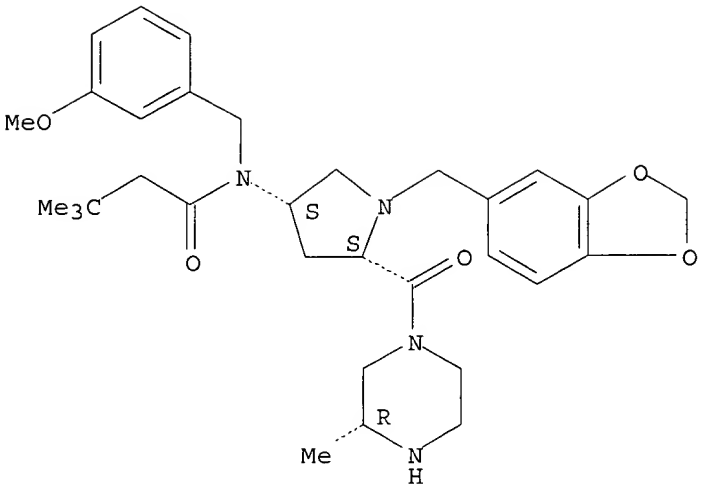
RN 334999-00-7 CAPLUS
CN Butanamide, N-[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-[[(3S)-3-methyl-1-piperazinyl]carbonyl]-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 334999-03-0 CAPLUS
CN Butanamide, N-[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-[[(3R)-3-methyl-1-piperazinyl]carbonyl]-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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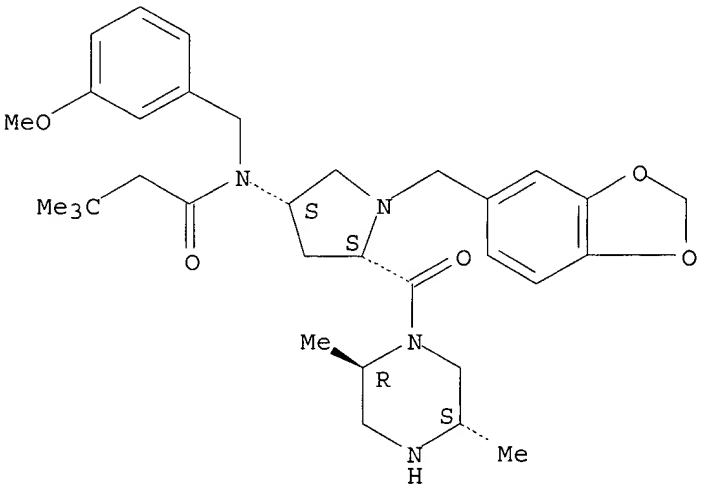
Absolute stereochemistry.



L6 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2003 ACS
AN 2002:293442 CAPLUS
DN 136:325823
TI Preparation and formulation of proline derivatives as mediators of hedgehog signaling pathways for pharmaceutical and cosmetic uses
IN Baxter, Anthony D.; Boyd, Edward A.; Guicherit, Oivin M.; Price, Stephen; Rubin, Lee D.
PA Curis, Inc., USA
SO PCT Int. Appl., 230 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-40
ICS A61K031-495; A61K009-08
CC 34-2 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 62, 63
FAN.CNT 2

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PI	WO 2002030421	A2	20020418	WO 2001-US32054	20011012
	WO 2002030421	A3	20020926		
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	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
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	US 2002165221	A1	20021107	US 2001-977096	20011012
PRAI	US 2000-240536P	P	20001013		
	US 2000-240564P	P	20001013		
	WO 2001-US32054	W	20011012		

OS MARPAT 136:325823
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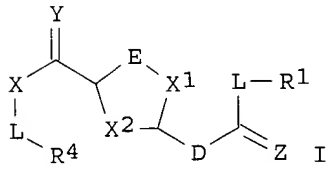

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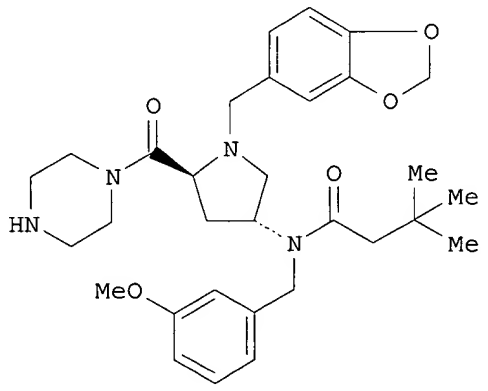


II

AB Proline-based compds. such as I [R1, R4 = H, alkyl, (CH2)n-(hetero)aryl (n = 0-5); L = null, -(CH2)n-, -alkenyl-, -alkynyl-, -(CH2)n-alkenyl-,

-(CH2)n-alkynyl-, -(CH2)nO(CH2)p-, -(CH2)nNR8(CH2)p-, -(CH2)nS(CH2)p-, -(CH2)nalkenyl(CH2)p-, -(CH2)nalkynyl(CH2)p-, -O(CH2)n-,-NR8(CH2)n-, or -S(CH2)n- (R8 is any group given for R1 or two R8 together may form a 4- to 8-membered ring; p = 0-3); X, D = NR8, O, S, NR8NR8, ONR8, or a direct bond; Y, Z = O or S; E represents NR5, where R5 represents LR8 or an ammonium salt; X1, X2 = null, CH2 or CH2CH2] were prepd. for pharmaceutical and cosmetic use. Thus, proline deriv. II was prepd. via a multistep synthetic sequence which started with trans-4-hydroxy-L-proline, 3-methoxybenzaldehyde, piperonal, tert-butylacetyl chloride, and N-(tert-butoxycarbonyl)piperazine. The prepd. proline derivs. were tested for agonist activity for inhibiting aberrant growth states resulting from hedgehog gain-of-function, ptc loss-of-function or smoothened gain-of-function comprising contacting the cell with a hedgehog antagonist, such as a small mol., in a sufficient amt. to aberrant growth state, e.g., to agonize a normal ptc pathway or antagonize smoothened or hedgehog activity.

ST proline deriv prepn hedgehog signaling pathway mediator; cosmetic proline deriv prepn hedgehog signaling pathway mediator; basal cell carcinoma preventative proline deriv prepn; spermatogenesis regulator proline deriv prepn; hematopoiesis regulator proline deriv prepn

IT Skin, neoplasm
(basal cell carcinoma, preventative; prepn. and formulation of proline derivs. for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

IT Cosmetics
(prepn. and formulation of proline derivs. for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

IT Hematopoiesis
Spermatogenesis
(regulators; prepn. and formulation of proline derivs. for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

IT Hedgehog protein
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(sonic; prepn. and formulation of proline derivs. for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

IT **334999-41-6P 334999-57-4P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. and formulation of proline derivs. for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

IT 334998-24-2P 334998-25-3P 334998-26-4P **334998-27-5P**
334998-28-6P 334998-29-7P 334998-30-0P 334998-31-1P 334998-32-2P
334998-33-3P 334998-34-4P 334998-35-5P **334998-36-6P**
334998-37-7P 334998-38-8P 334998-39-9P 334998-40-2P
334998-41-3P 334998-42-4P 334998-43-5P 334998-44-6P 334998-45-7P
334998-46-8P 334998-47-9P 334998-48-0P 334998-49-1P 334998-50-4P
334998-51-5P 334998-52-6P 334998-53-7P 334998-54-8P 334998-55-9P
334998-56-0P 334998-57-1P 334998-58-2P 334998-59-3P 334998-60-6P
334998-61-7P 334998-62-8P 334998-63-9P 334998-64-0P 334998-65-1P
334998-66-2P 334998-67-3P 334998-68-4P 334998-69-5P 334998-70-8P
334998-71-9P 334998-72-0P 334998-73-1P 334998-74-2P 334998-75-3P
334998-76-4P 334998-77-5P 334998-78-6P 334998-79-7P 334998-80-0P
334998-81-1P 334998-82-2P 334998-83-3P 334998-84-4P 334998-85-5P
334998-86-6P 334998-87-7P 334998-88-8P 334998-89-9P 334998-90-2P
334998-91-3P 334998-92-4P 334998-93-5P 334998-94-6P 334998-95-7P
334998-96-8P 334998-97-9P 334998-98-0P 334998-99-1P
334999-00-7P 334999-03-0P 334999-05-2P 334999-07-4P
334999-09-6P 334999-11-0P 334999-13-2P 334999-15-4P 334999-17-6P
334999-19-8P 334999-21-2P 334999-24-5P 334999-94-9P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. and formulation of proline derivs. for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

IT 51-35-4 591-31-1 623-05-2 7065-46-5 7693-46-1 57260-71-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. and formulation of proline derivs. for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

IT 623-05-2DP, polymer bound 40216-83-9P 74844-91-0P 84520-67-2P 84520-68-3P 121147-97-5P 121148-01-4P 334999-29-0P 334999-32-5P 334999-33-6P 334999-34-7P 334999-35-8P 334999-36-9P 334999-37-0P 334999-38-1P 334999-39-2P 334999-43-8P 334999-45-0P 334999-47-2P 334999-48-3P 334999-51-8P 334999-53-0P 334999-55-2P 334999-60-9DP, polymer bound
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and formulation of proline derivs. for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

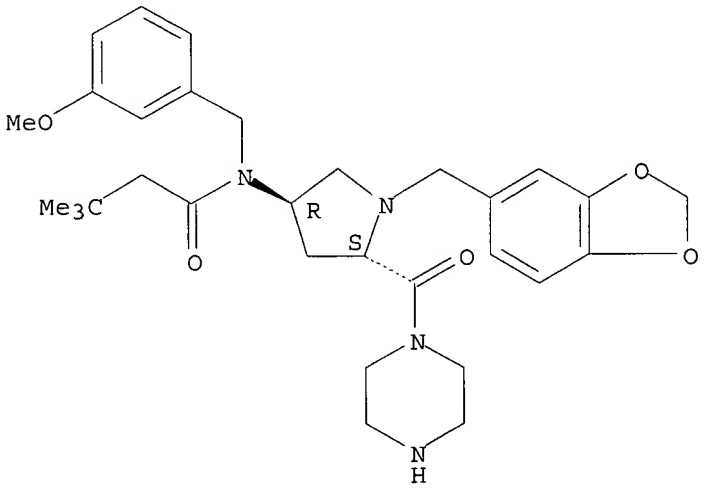
IT **334999-41-6P 334999-57-4P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. and formulation of proline derivs. for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)

RN 334999-41-6 CAPLUS
CN Butanamide, N-[(3R,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl-, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

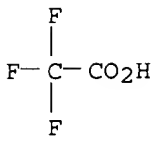
CRN 334998-37-7
CMF C31 H42 N4 O5

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

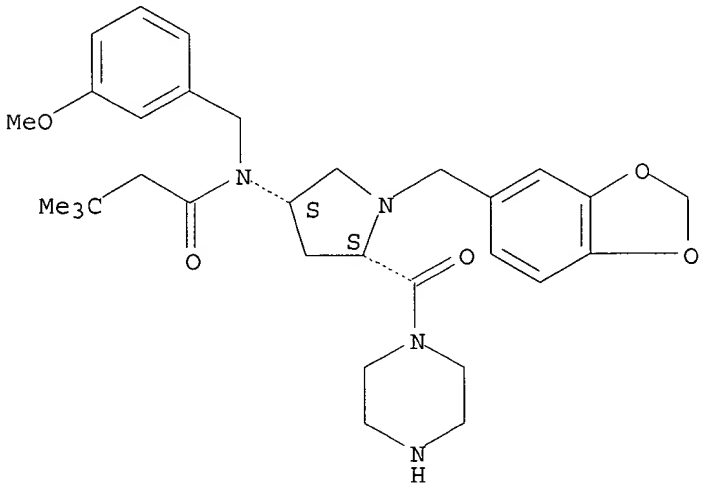


RN 334999-57-4 CAPLUS
CN Butanamide, N-[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl-, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

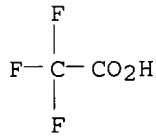
CRN 334998-36-6
CMF C31 H42 N4 O5

Absolute stereochemistry.



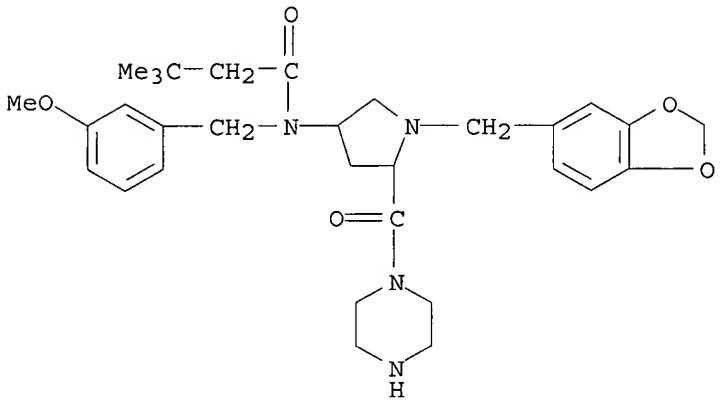
CM 2

CRN 76-05-1
CMF C2 H F3 O2



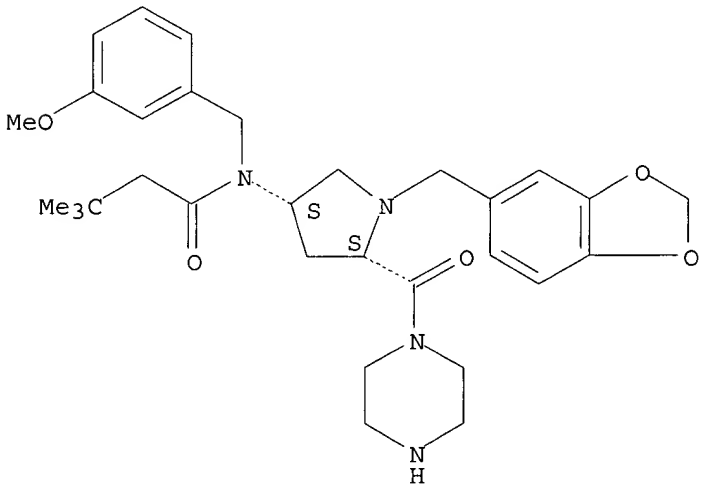
IT **334998-27-5P 334998-36-6P 334998-37-7P**
334999-00-7P 334999-03-0P 334999-19-8P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and formulation of proline derivs. for pharmaceutical and cosmetic uses as mediators of hedgehog signaling pathways)
RN 334998-27-5 CAPLUS
CN Butanamide, N-[1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-

pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl- (9CI) (CA INDEX NAME)



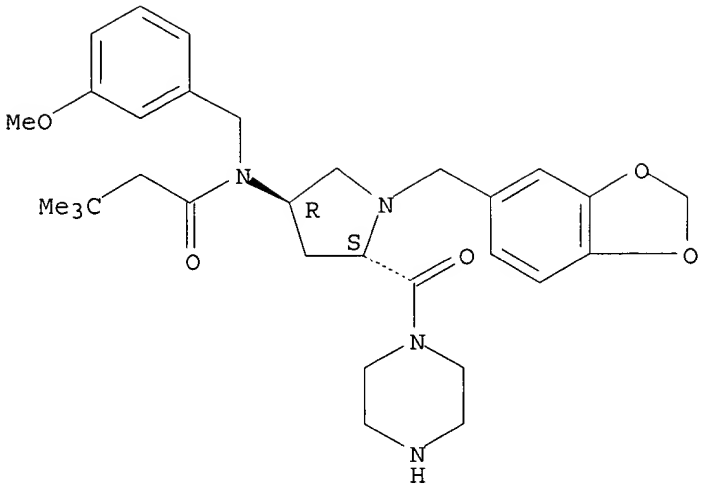
RN 334998-36-6 CAPLUS
CN Butanamide, N-[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



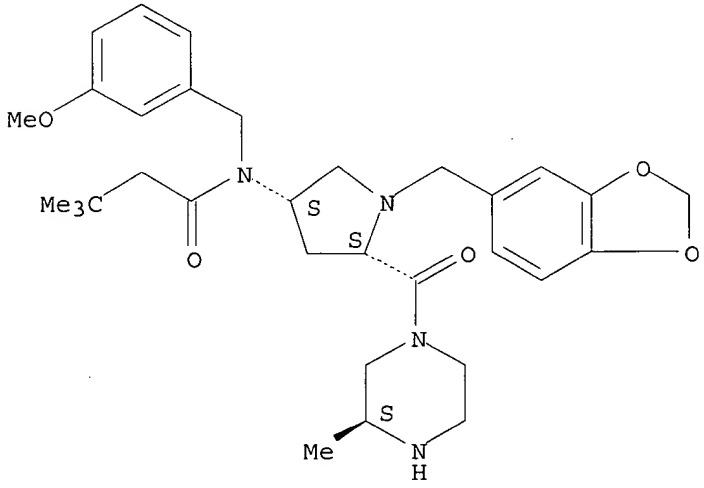
RN 334998-37-7 CAPLUS
CN Butanamide, N-[(3R,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



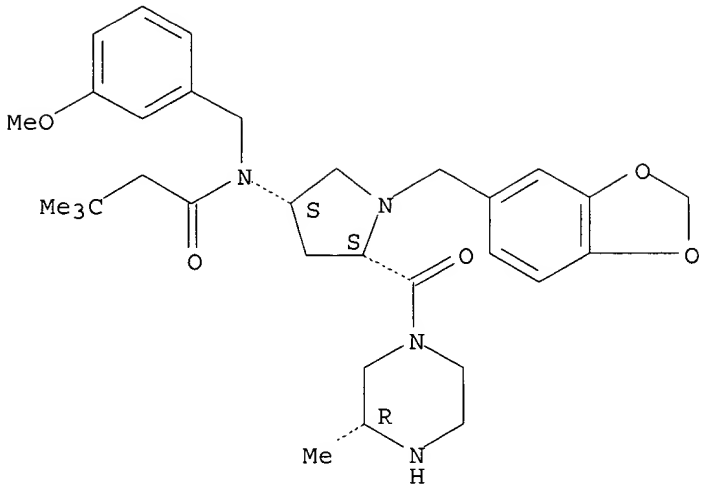
RN 334999-00-7 CAPLUS
CN Butanamide, N-[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-[[(3S)-3-methyl-1-piperazinyl]carbonyl]-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



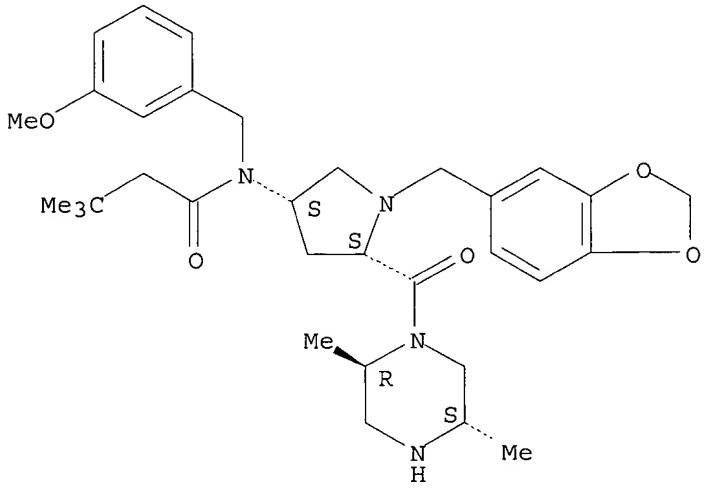
RN 334999-03-0 CAPLUS
CN Butanamide, N-[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-[[(3R)-3-methyl-1-piperazinyl]carbonyl]-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 334999-19-8 CAPLUS
CN Butanamide, N-[(3S,5S)-1-(1,3-benzodioxol-5-ylmethyl)-5-[[(2R,5S)-2,5-dimethyl-1-piperazinyl]carbonyl]-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L6 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2003 ACS
AN 2002:293477 CAPLUS
DN 136:304056
TI Hedgehog antagonists, methods and uses related thereto
IN Dudek, Henryk; Pepicelli, Carmen; Karavanov, Irina
PA Curis, Inc., USA
SO PCT Int. Appl., 224 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K039-395
CC 1-6 (Pharmacology)
Section cross-reference(s): 9, 14
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002030462	A2	20020418	WO 2001-US32100	20011015
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2002165221	A1	20021107	US 2001-977096	20011012
	AU 2001096844	A5	20020422	AU 2001-96844	20011015
PRAI	US 2000-240564P	P	20001013		
	US 2000-240536P	P	20001013		
	WO 2001-US32100	W	20011015		

AB The present application is directed to compns. and methods for inhibiting angiogenesis and treating or preventing unwanted cell proliferation, including tumors, by inhibiting the hedgehog pathway, e.g., with an antagonist of the hedgehog pathway such as those disclosed herein. In one embodiment, the subject methods may be used to inhibit unwanted cell proliferation by detg. whether cells overexpress a gli gene, and contacting cells that overexpress gli gene with an effective amt. of a hedgehog antagonist. In preferred embodiments ,the unwanted cell proliferation is cancer or benign prostatic hyperplasia. Another aspect of the present invention involves measuring the levels of gli gene expression in order detn. the likelihood that a cancer will develop or to detn. a cancer treatment protocol. Another embodiment of the invention involves methods for using hedgehog antagonists to stimulate surfactant prodn. or lamellated body formation in lung cells, esp. the lung cells of premature infants. In other preferred embodiments, hedgehog antagonists are selected from small mols., hedgehog antibodies, antisense nucleic acids and ribozymes.

ST hedgehog pathway antagonist antiproliferative agent gli gene; lung surfactant prodn hedgehog pathway antagonist

IT Lung, neoplasm
(adenocarcinoma, alveolar; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Prostate gland
(adenocarcinoma, inhibitors; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Antitumor agents
(adenocarcinoma; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Prostate gland
(benign hyperplasia, inhibition; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)
IT Antitumor agents
(bladder carcinoma; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)
IT Antitumor agents
(bronchi carcinoma, adenocarcinoma; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)
IT Diagnosis
(cancer; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)
IT Bronchi
(carcinoma, inhibitors, adenocarcinoma; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)
IT Bladder
Mammary gland
(carcinoma, inhibitors; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)
IT Intestine, neoplasm
(colon, inhibitors; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)
IT Antitumor agents
(colon; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)
IT Neoplasm
(diagnosis; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)
IT Antitumor agents
(genitourinary tract tumor inhibitors; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gli-1; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gli; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)
IT Antitumor agents
Cytotoxic agents
Drug screening
High throughput screening
Human
Signal transduction, biological
Surfactants
(hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate

surfactant prodn. in lung for treatment of premature infants)

IT Hedgehog protein
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Antisense oligonucleotides
Ribozymes
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Embryo, animal
(hedgehog signaling pathway in maturation of; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Lung, neoplasm
Neoplasm
(hedgehog signaling pathway in; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Lung, neoplasm
(inhibitors; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Lung
(lamellated body formation and surfactant prodn. in; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Antitumor agents
(lung small-cell carcinoma; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Antitumor agents
(lung; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Antitumor agents
(mammary gland carcinoma; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Antitumor agents
(mammary gland; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Bladder
Mammary gland
Prostate gland
(neoplasm, hedgehog signaling pathway in; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Mammary gland
Prostate gland
(neoplasm, inhibitors; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Mutation
(of hedgehog protein; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to

stimulate surfactant prodn. in lung for treatment of premature infants)

IT Newborn
(premature; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Antitumor agents
(prostate adenocarcinoma; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Antitumor agents
(prostate gland; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Lung, neoplasm
(small-cell carcinoma, inhibitors; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Hedgehog protein
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(sonic; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT Antibodies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(to hedgehog protein; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

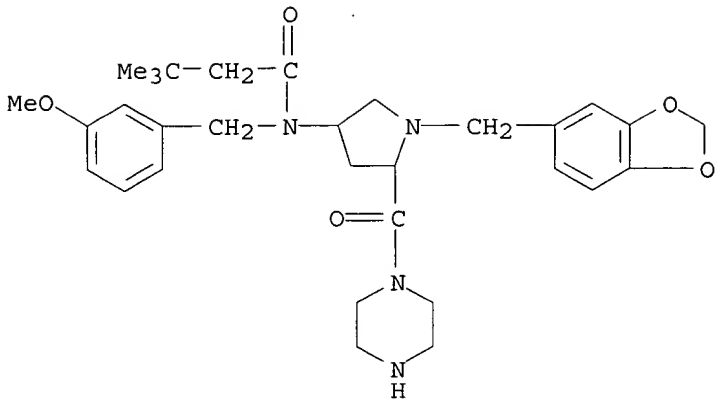
IT Urogenital tract
(tumor inhibitors; hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT 77-59-8, Tomatidine 78-41-1, Triparanol 366-93-8, AY9944 469-59-0, Jervine 4449-51-8, Cyclopamine 330796-27-5 **334998-27-5**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

IT **334998-27-5**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

RN 334998-27-5 CAPLUS

CN Butanamide, N-[1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl- (9CI) (CA INDEX NAME)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Me3C— CH2— C
MeO
CH2— N
N— CH2
O
O
O= C
N
N
H

IT 77-59-8, Tomatidine 78-41-1, Triparanol 366-93-8, AY9944 469-59-0, Jervine 4449-51-8, Cyclopamine 330796-27-5 **334998-27-5**
(hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

ACCESSION NUMBER: 2002:295175 USPATFULL
TITLE: Mediators of hedgehog signaling pathways, compositions and uses related thereto
INVENTOR(S): Baxter, Anthony David, Hertfordshire, UNITED KINGDOM
Boyd, Edward Andrew, Oxfordshire, UNITED KINGDOM
Guicherit, Oivin M., Belmont, MA, UNITED STATES
Price, Stephen, Buckinghamshire, UNITED KINGDOM
Rubin, Lee L., Wellesley, MA, UNITED STATES

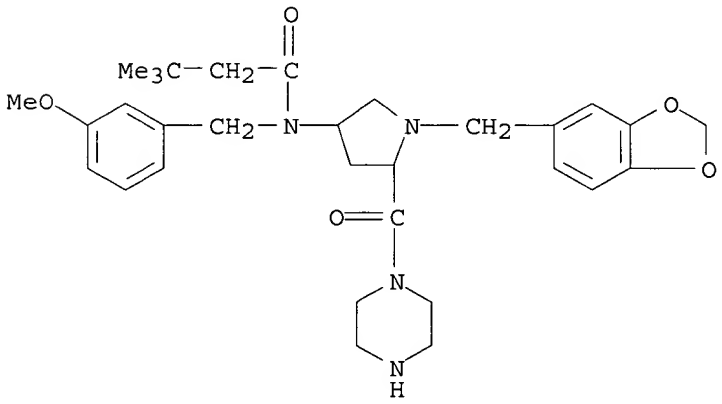
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002165221	A1	20021107
APPLICATION INFO.:	US 2001-977096	A1	20011012 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-240536P	20001013 (60)
	US 2000-240564P	20001013 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: ROPES & GRAY, ONE INTERNATIONAL PLACE, BOSTON, MA, 02110-2624
NUMBER OF CLAIMS: 92
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 58 Drawing Page(s)
LINE COUNT: 5140
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **334998-27-5**
(hedgehog pathway antagonists for inhibition of unwanted cell proliferation in cells overexpressing gli gene or to stimulate surfactant prodn. in lung for treatment of premature infants)

RN 334998-27-5 USPATFULL
CN Butanamide, N-[1-(1,3-benzodioxol-5-ylmethyl)-5-(1-piperazinylcarbonyl)-3-pyrrolidinyl]-N-[(3-methoxyphenyl)methyl]-3,3-dimethyl- (9CI) (CA INDEX NAME)



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